Identifying individuals with advanced chronic conditions who may benefit from an early palliative care approach

Using the NECPAL CCOMS-ICO© tool:
population-based prevalence,
predictive validity for mortality and
predictive models

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The research presented in this thesis was conducted within the Chair in Palliative Care, Centre for Health and Social Care Research, at the University of Vic ï Central University of Catalonia, and the ǿQUALYô Observatory, WHO Collaborating Center for Public Health Palliative Care Programmes, at the Catalan Institute of Oncology, Catalonia, Spain.

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KINDNESS

ñThree things in human life are important: the first is to be kind; the second is to be kind; and the third is to be kind.ò

Henry James

ñTenderness and kindness are not signs of weakness and despair, but manifestations of strength and resolution.ò

Kahlil Gibran

ñThe true essence of humankind is kindness. There are other qualities which come from education or knowledge, but it is essential, if one wishes to be a genuine human being and impart satisfying meaning to oneôs existence, to have a good heart.ò

Tenzin Gyatso, the 14th Dalai Lama

To my father, a goodhearted man,
who could not see it and so happy would have made him.

To my son,
who has inherited his grandfatherôs good heart.

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I. Abstract

Background

In high income countries, around 75% of the population will die due to chronic conditions. Despite only about one third of those having chronic diseases needing palliative care suffer from cancer, palliative care is mainly aimed at patients with terminal cancer in institutional settings. Nevertheless, there is strong evidence of unmet palliative needs among people with life-threatening non-malignant disease.

Data in patients with advanced cancer show that early provision of specialty palliative care improves quality of life, lowers spending, and helps clarify treatment preferences and goals of care. Translating available evidence into health systems to deliver early palliative care to all people with advanced chronic conditions different than cancer in any setting of care might improve clinical outcomes decreasing costs of care in this population.

Recognising transition 1, the period referred to as end of life preceding terminal phase, may enable early palliative care intervention and anticipatory palliative care planning. Nevertheless, the right moment to start palliative care -for which early identification is a prerequisite- has not been defined yet.

Acknowledging limitations of available prognostic indices and predictive models, with insufficient evidence at this time to recommend their widespread use, a pragmatic approach to identify candidates for palliative care advocating a person centred approach based not on diagnosis or prognosis, but on their needs has been proposed. It is based on asking the surprise question (ñWould you be surprised if this patient were to die in the next 12 months?ò) and looking for one or more clinical indicators that would suggest a person might be at risk of deteriorating and dying and should be assessed for unmet needs.

This pragmatic approach is the basis of most of the set of identification indicators which have been developed in recent years to recognizing transition 1 and

identifying individuals likely in need of palliative care, as the NECPAL CCOMS-ICO© tool.

The overall aim of this thesis was to evaluate the usefulness of the NECPAL CCOMS-ICO© tool in identifying individuals with advanced chronic conditions who may benefit from an early palliative care approach, through employing it as a tool to determine the population-based prevalence of these individuals *(Study I)*, evaluating its predictive validity for mortality at 3, 6, 12 and 24 months to inform usefulness as screening tool for early palliative care *(Study II)* and identifying the indicators that were associated with mortality within 24 months to develop a predictive model for identifying individuals at high risk of death *(Study III)*.

Methods

Study I is a cross-sectional, population-based study.

Case identification was undertaken in the County of Osona, located north of Barcelona, in a) 3 randomly selected primary care centres -i.e. 51595 registered inhabitants-, b) all inpatient units of acute bed hospital, c) all inpatient units of intermediate care centre, and d) nursing homes, serving these 3 primary care centres. Cases were identified by healthcare professionals (physicians and nurses) in each health facility. Recruited individuals were assessed by employing the NECPAL CCOMS-ICO© tool and categorised as surprise question positive (SQ+) when, at least, one of the attending healthcare professionalsô answer was ñnoò to the surprise question. SQ+ individuals were also considered as NECPAL+ when they presented, at least, one positive additional indicator from among the remaining ones. All individuals classified as NECPAL+ were considered likely in need of palliative care.

Study II is a longitudinal, prospective, cohort study. Individuals from previous population-based prevalence study that died during the 2-year study period were identified.

Study III is a longitudinal, prospective, cohort study. Indicators included in the NECPAL CCOMS-ICO© tool and mortality status at 3, 6, 12 and 24 months were analysed in the whole cohort of individuals recruited in previous population-based prevalence study.

Results

Study I: A total number of 1063 individuals with advanced chronic conditions were recruited. 840 were identified as SQ+, among which 783 were also identified as NECPAL+. Population-based prevalence of individuals with advanced chronic conditions who may benefit from an early palliative care approach, that is to say NECPAL+ individuals, was 1.5%. Almost two thirds were female and the mean age was 81 years old. The vast majority were living at home (66.9%) or nursing homes (19.6%). The most prevalent conditions among NECPAL+ individuals were organ failure (32.3%) and advanced frailty (31.4%), followed by dementia (23.4%). Cancer is the less prevalent disease among individuals with advanced chronic conditions who may benefit from an early palliative care approach (12.9%).

Study II: A total of 1059 individuals were available for survival analysis. At 12 months, the NECPAL CCOMS-ICO© tool presents very high sensitivity (91.3, CI: 87.2-94.2) and very high negative predictive value (NPV) (91.0, CI: 86.9-94.0), with low specificity (32.9, CI: 29.6-36.3), explained by high number of false positives, and low positive predictive value (PPV) (33.5, CI: 30.2-36.9), explained by low number of true positives (low mortality rate) and high number of false positives. At 24 months, it improves specificity (35.0, CI: 31.3-38.7) and PPV (45.8, CI: 42.3-49.3), although they remain low, decreasing sensitivity (87.5, CI: 84.3-90.7) and NPV (81.7, CI: 77.2-86.2).

Per advanced chronic condition, sensitivity and NPV were similarly high, with low specificity. PPV were higher in cancer (64.4, CI: 54.1-73.5 at 12 months; 71.3, CI: 61.3-79.6 at 24 months), followed by dementia (36.5, CI: 29.5-44.0 at 12 months; 56.4, CI: 48.8-63.6 at 24 months) and organ failure (30.4, CI: 24.9-36.6 at

12 months; 45.8, CI: 42.3-49.3 at 24 months) and, finally, advanced frailty (21.6, CI: 16.8-27.4 at 12 months; 30.6, CI: 25.0-36.9 at 24 months).

Per setting of care, sensitivity and NPV were similarly high, with low specificity. PPV is higher in intermediate care centre (67.3, CI: 53.2-79.0 at 12 months; 70.9, CI: 56.9-82.0 at 24 months) and acute bed hospital (54.0, CI: 39.5-67.9 at 12 months; 62.0, CI: 47.2-75.0 at 24 months), followed by nursing homes (33.1, CI: 25.9-41.2 at 12 months; 57.8, CI: 49.6-65.6 at 24 months) and, finally, primary care centres (28.0, CI: 24.2-32.1 at 12 months; 38.0, CI: 33.8-42.3 at 24 months).

The predictive validity for mortality of the NECPAL CCOMS-ICO© tool and the SQ was non-significantly different, neither in the whole population-based sample, nor in subgroups by advanced chronic condition and setting of care.

Study III: The indicators associated with mortality within 24 months among those included in the NECPAL CCOMS-ICO© tool vary according to advanced chronic condition and setting of care. Two simple predictive models were developed. The first one, in advanced frailty; the second one, in organ failure.

Advanced frailty: In the multivariate Cox model, infections with systemic impact (HR 4.11, 95% CI 1.68-10.01), confusional syndrome (HR 2.73, 95% CI 1.71-4.36), identification of palliative care needs by healthcare professionals (HR 2.70, 95% CI 1.33-5.52) and complex/intense nursing care needs (HR 2.35, 95% CI 1.36-4.06) were the indicators included in the NECPAL CCOMS-ICO© tool associated with a higher risk of mortality. Some other indicators, as falls (HR 1.95, 95% CI 1.08-3.50), co-morbidity (Charlson index, HR 1.16, 95% CI 1.05-1.27), urgent admissions (HR 1.11, 95% CI 1.01-1.23) and age (HR 1.05, 95% CI 1.02-1.09) were also associated with an increased risk of death within 24 months after identification.

The AUC showed outstanding discrimination at 3 months [0.92 (95% CI 0.85-0.99)], with highest concurrent sensitivity and specificity above 80%, and acceptable discrimination at 6, 12 and 24 months [0.79 (95% CI 0.70-0.87), 0.73 (95% CI 0.65-0.81) and 0.72 (95% CI 0.66-0.78), respectively]. At 6 and 12

months, highest concurrent sensitivity and specificity were above 70%, decreasing below this threshold only at 24 months.

Organ failure: In the multivariate Cox model, the surprise question (HR 3.07, 95% CI 1.54-6.15), infections with systemic impact (HR 2.96, 95% CI 1.66-5.26) and carerôs request for palliative care approach (HR 2.31, 95% CI 1.47-3.61) were the indicators included in the NECPAL CCOMS-ICO© tool associated with a higher risk of mortality. Some other indicators, as falls (HR 1.99, 95% CI 1.03-3.86), severe dependency (HR 1.87, 95% CI 1.07-3.27), confusional syndrome (HR 1.74, 95% CI 1.07-2.83), complex/intense nursing care needs (HR 1.69, 95% CI 1.08-2.65) and age (HR 1.02, 95% CI 1.003-1.04) were also associated with an increased risk of death within 24 months after identification.

The AUC showed excellent discrimination at 3 months [0.81 (95% CI 0.71-0.91)], with highest concurrent sensitivity and specificity around 70%, and acceptable discrimination at 6 and 12 months [0.79 (95% CI 0.70-0.88) and 0.74 (95% CI 0.67-0.81), respectively], with a slightly increase in the AUC at 24 months [0.75 (95% CI 0.69-0.80). At 6 and 24 months, highest concurrent sensitivity and specificity were around 70%. The modelôs discrimination ability showed its worse AUC, sensitivity and specificity at 12 months.

Conclusions

The NECPAL CCOMS-ICO© tool can be considered useful in identifying individuals with advanced chronic conditions who may benefit from an early palliative care approach.

It can be employed to assess the population-based needs for palliative care through identifying prospectively the population-based prevalence of this population, an innovative approach which can be potentially useful for improving clinical practice.

It can be used, as well as the SQ, as screening tool for early palliative care. They present high sensitivity and high NPV, both important predictive values to

identify such a vulnerable and often undetected and under-treated population. They can be employed as a first assessment to identify this population, preferably accompanied by repeated or additional tests, aiming to improve specificity.

From a population-based perspective, end of life trajectories may turn out to be an excellent conceptual framework for the development of simple predictive models to identify individuals at high risk of death, particularly in advanced frailty and organ failure, the most prevalent population-based advanced chronic conditions, for which simple and promising predictive models have been developed and should be externally validated.

II. Abstract (Catalan version)

Antecedents

Als països desenvolupats, al voltant del 75% de la població morirà degut a malalties cròniques. Malgrat només un terç dels que tenen malalties cròniques i necessiten atenció pal·liativa pateix càncer, les cures pal·liatives estan dirigides principalment als pacients amb càncer terminal en entorns institucionals. No obstant això , hi ha una forta evidència de les necessitats pal·liatives no satisfetes entre les persones amb malaltia no maligna amenaçant per a la vida.

Les dades en pacients amb càncer avançat mostren que la provisió precoç de cures pal·liatives especialitzades milloren la qualitat de vida, disminueix la despesa i ajuda a clarificar les preferències de tractament i els objectius dôatenció. Traslladar lôevidència disponible als sistemes de salut per oferir atenció pal·liativa precoç a totes les persones amb condicions cròniques diferents del càncer a qualsevol dispositiu dôatenció podria millorar els resultats clínics disminuint els costos dôatenció en aquesta població.

Reconèixer la primera transició, el període referit com a final de vida, que precedeix la fase terminal, podria possibilitar la intervenció pal·liativa precoç i la planificació de decisions anticipada. Tot i així, el moment adequat per a començar lôatenció pal·liativa -per a la què la identificació precoç és un prerequisit- no ha estat definit encara.

Admetent limitacions dôíndex pronòstics i models predictius disponibles, amb evidència insuficient actualment per a recomanar el seu ús generalitzat, un abordatge pragmàtic per a identificar candidats per a atenció pal·liativa defensant un abordatge centrat en la persona basat no en el diagnòstic o el pronòstic, sinó en les seves necessitats ha estat proposat. Està basat en preguntar la pregunta sorpresa (ñEl sorprendria que aquest pacient morís en els propers 12 mesos?ò) i la cerca dôun o més indicadors clínics que podrien suggerir que una persona podria

estar en risc de deteriorament i mort i hauria de ser avaluada per a necessitats no satisfetes.

Aquest abordatge pragmàtic és el fonament de la majoria dels sets d'indicadors d'identificació que han estat desenvolupats en els últims anys per a reconèixer la 1a transició i identificar individus amb probable necessitat d'atenció pal·liativa, com ara l'instrument NECPAL CCOMS-ICO©.

L'objectiu general d'aquesta tesi és avaluar la utilitat de l'instrument NECPAL CCOMS-ICO© per a identificar individus amb condicions cròniques avançades que es podrien beneficiar d'un abordatge pal·liatiu precoç, a través de la seva utilització per a determinar la prevalença poblacional d'aquests individus *(Estudi I)*, avaluant la seva validesa predictiva per a mortalitat a 3, 6, 12 i 24 mesos per a informar la seva utilitat com a instrument de cribratge per a atenció pal·liativa precoç *(Estudi II)* i identificant indicadors associats amb mortalitat en 24 mesos per a desenvolupar un model predictiu per a la identificació d'individus en alt risc de mort *(Estudi III)*.

Metodologia

L'estudi I és un estudi poblacional de tall transversal.

La identificació de casos es va dur a terme a la comarca d'Osona, al nord de Barcelona, a a) 3 centres d'atenció primària seleccionats aleatòriament -51595 habitants registrats-, b) tots els pacients ingressats a l'hospital d'aguts, c) tots els pacients ingressats al centre sociosanitari i d) les residències, que servien aquests 3 centres d'atenció primària. Els casos van ser identificats pels professionals sanitaris (metges i infermeres) a cada recurs d'atenció. Els individus reclutats van ser avaluats emprant l'instrument NECPAL CCOMS-ICO© i categoritzats com a pregunta sorpresa positiu (PS+) quan, almenys, un dels professionals sanitaris va respondre ñnoò a la pregunta sorpresa. Els individus PS+ van ser considerats com a NECPAL+ si van presentar, almenys, un indicador positiu addicional de entre

els restants. Tots els individus classificats com a NECPAL+ van ser considerats com a individus amb probable necessitat dôatenció pal·liativa.

Lôestudi II és un estudi de cohort, prospectiu, longitudinal. Els individus de lôestudi previ de prevalença poblacional que van morir al llarg dels 2 anys de seguiment de lôestudi van ser identificats.

Lôestudi III és un estudi de cohort, prospectiu, longitudinal. Els indicadors de lôinstrument NECPAL CCOMS-ICO© i la mortalitat a 3, 6, 12 i 24 mesos van ser analitzats en la totalitat de la cohort reclutada en lôestudi previ de prevalença poblacional.

Resultats

Estudi I: Un total de 1063 individus amb condicions cròniques avançades van ser reclutats. 840 van ser identificats com PS+, entre els que 783 van ser també identificats com a NECPAL+. La prevalença poblacional dôindividus amb condicions cròniques avançades que es podrien beneficiar dôun abordatge pal·liatiu precoç, és a dir individus NECPAL+, va ser 1.5%. Quasi dos terços eren dones i lôedat mitjana va ser de 81 anys. La gran majoria viuen als seus domicilis (66.9%) o a residencies (19.6%). Les condicions més prevalents entre els individus NECPAL+ van ser malaltia dôòrgan (32.3%) i fragilitat avançada (31.4%), seguides de demència (23.4%). El càncer és la malaltia menys prevalent entre els individus amb condicions cròniques avançades que es podrien beneficiar dôun abordatge pal·liatiu (12.9%).

Estudi II: Un total de 1059 individus van ser seguits per a lôanàlisi de supervivència. A 12 mesos, lôinstrument NECPAL CCOMS-ICO© presenta una molta alta sensibilitat (91.3, IC: 87.2-94.2) i un molt alt valor predictiu negatiu (VPN) (91.0, IC: 86.9-94.0), amb baixa especificitat (32.9, IC: 29.6-36.3), explicada per lôalt nombre de falsos positius, i baix valor predictiu positiu (VPP) (33.5, IC: 30.2-36.9), explicat pel baix nombre de veritables positius (baixa taxa de mortalitat) i lôalt nombre de falsos positius. A 24 mesos, millora lôespecificitat

(35.0, IC: 31.3-38.7) i el VPP (45.8, IC: 42.3-49.3), tot i que continuen sent baixos, disminuint la sensibilitat (87.5, IC: 84.3-90.7) i el VPN (81.7, IC: 77.2-86.2).

Per condició crònica avançada, la sensibilitat i el VPN van ser igualment alts, amb baixa especificitat. El VPP va ser més alt en càncer (64.4, IC: 54.1-73.5 a 12 mesos; 71.3, IC: 61.3-79.6 a 24 mesos), seguit per demència (36.5, IC: 29.5-44.0 a 12 mesos; 56.4, IC: 48.8-63.6 a 24 mesos) i malaltia dôòrgan (30.4, IC: 24.9-36.6 a 12 mesos; 45.8, IC: 42.3-49.3 a 24 mesos) i, finalment, fragilitat avançada (21.6, IC: 16.8-27.4 a 12 mesos; 30.6, IC: 25.0-36.9 a 24 mesos).

Per recurs dôatenció, la sensibilitat i el VPN van ser igualment alts, amb baixa especificitat. El VPP va ser més alt al centre sociosanitari (67.3, IC: 53.2-79.0 a 12 mesos; 70.9, IC: 56.9-82.0 a 24 mesos) i a lôhospital dôaguts (54.0, IC: 39.5-67.9 a 12 mesos; 62.0, IC: 47.2-75.0 a 24 mesos), seguit de les residències (33.1, IC: 25.9-41.2 a 12 mesos; 57.8, IC: 49.6-65.6 a 24 mesos) i, finalment, els centres dôatenció primària (28.0, IC: 24.2-32.1 a 12 mesos; 38.0, IC: 33.8-42.3 a 24 mesos).

La validesa predictiva per a mortalitat de lôinstrument NECPAL CCOMS-ICO© i la PS no és significativament diferent, ni a la mostra poblacional ni en els subgrups per condició crònica avançada i recurs dôatenció.

Estudi III: Els indicadors de lôinstrument NECPAL CCOMS-ICO© associats amb mortalitat en 24 mesos varien en funció de la condició crònica avançada i segons el recurs dôatenció. Dos models predictius simples han estat desenvolupats. El primer, en fragilitat avançada; el segon, en malaltia dôòrgan.

Fragilitat avançada: En el model multivariat de Cox, les infeccions amb afectació sistèmica (HR 4.11, 95% IC 1.68-10.01), la síndrome confusional (HR 2.73, 95% IC 1.71-4.36), la identificació de necessitats dôatenció pal·liativa per part dels professionals sanitaris (HR 2.70, 95% IC 1.33-5.52) i la necessitat de cures infermeres complexes/intenses (HR 2.35, 95% IC 1.36-4.06) van ser els indicadors de lôinstrument NECPAL CCOMS-ICO© associats amb un risc més alt

de mortalitat. Altres indicadors, com les caigudes (HR 1.95, 95% IC 1.08-3.50), la comorbiditat (índex de Charlson, HR 1.16, 95% IC 1.05-1.27), els ingressos urgents (HR 1.11, 95% IC 1.01-1.23) i lôedat (HR 1.05, 95% IC 1.02-1.09) estan associats també amb un risc augmentat de mort en 24 mesos després de la identificació.

LôAUC va mostrar una discriminació excel·lent a 3 mesos [0.92 (95% IC 0.85-0.99)], amb la major sensibilitat i especificitat concurrent per sobre del 80%, i una discriminació acceptable a 6, 12 i 24 mesos [0.79 (95% IC 0.70-0.87), 0.73 (95% IC 0.65-0.81) i 0.72 (95% IC 0.66-0.78), respectivament]. A 6 i 12 mesos, la major sensibilitat i especificitat concurrent va ser superior al 70%, disminuint per sota dôaquest llindar només a 24 mesos.

Malaltia dôòrgan: En el model multivariat de Cox,, la pregunta sorpresa (HR 3.07, 95% IC 1.54-6.15), les infeccions amb afectació sistèmica (HR 2.96, 95% IC 1.66-5.26) i la demanda del cuidador dôun abordatge pal·liatiu (HR 2.31, 95% IC 1.47-3.61) van ser els indicadors de lôinstrument NECPAL CCOMS-ICO© associats amb un risc més alt de mortalitat. Altres indicadors, como les caigudes (HR 1.99, 95% IC 1.03-3.86), la dependència severa (HR 1.87, 95% IC 1.07-3.27), la síndrome confusional (HR 1.74, 95% IC 1.07-2.83), la necessitat de cures infermeres complexes/intenses (HR 1.69, 95% IC 1.08-2.65) i lôedat (HR 1.02, 95% IC 1.003-1.04) estan associats també amb un risc augmentat de mort en 24 mesos després de la identificació.

LôAUC va mostrar una discriminació molt bona a 3 mesos [0.81 (95% CI 0.71-0.91)], amb la major sensibilitat i especificitat concurrent al voltant del 70%, i una discriminació acceptable a 6 i 12 mesos [0.79 (95% CI 0.70-0.88) i 0.74 (95% CI 0.67-0.81), respectivament], amb un discret augment de lôAUC a 24 mesos [0.75 (95% CI 0.69-0.80). A 6 i 24 mesos, la major sensibilitat i especificitat concurrent va estar al voltant del 70%. Lôhabilitat de discriminació del model va mostrar la seva pitjor AUC, sensibilitat i especificitat a 12 mesos.

Conclusions

Lôinstrument NECPAL CCOMS-ICO© pot ser considerat útil per a identificar individus amb condicions cròniques avançades que es podrien beneficiar dôun abordatge pal·liatiu precoç.

Pot ser utilitzat per a avaluar les necessitats poblacionals dôatenció pal·liativa a través de la identificació prospectiva de la prevalença poblacional dôaquesta població, un abordatge innovador que, potencialment, pot ser útil per a millorar la pràctica clínica.

Pot ser utilitzat, de la mateixa manera que la PS, com a instrument de cribratge per a atenció pal·liativa precoç. Presenten alta sensibilitat i alt VPN, tots dos valors predictius importants per a identificar a aquesta vulnerable població, freqüentment no detectada i infratractada. Poden ser utilitzats com a primera mesura per a identificar aquesta població, preferentment acompanyat dôexploracions repetides o addicionals, per tal de millorar-ne lôespecificitat.

Des dôuna perspectiva poblacional, les trajectòries de final de vida podrien resultar ser un excel·lent marc conceptual per al desenvolupament de models predictius simples per a la identificació de persones en risc alt de mort, particularment en fragilitat avançada i malaltia dôòrgan, les condicions cròniques avançades poblacionals més prevalents, per a les què sôhan desenvolupat models predictius simples i prometedors que sôhaurien de validar externament.

III. List of papers

I. Gómez-Batiste X, Martinez-Muñoz M, Blay C et al. Prevalence and characteristics of patients with advanced chronic conditions in need of palliative care in the general population: A cross-sectional study. Palliat Med 2014; 28(4):302-311.

II. Gómez-Batiste X, Martinez-Muñoz M, Blay C et al. (2015). Utility of the NECPAL CCOMS-ICO© tool and the Surprise Question as screening tools for early palliative care and to predict 2-year mortality in patients with advanced chronic conditions: a cohort study. Manuscript submitted for publication.

III. Martinez-Muñoz M, Amblàs-Novellas J, Oller R, et al. (2016). Case finding for individuals with advanced chronic conditions at high risk of death in the next 24 months: development of a predictive model. Manuscript in preparation.

IV. Introduction

Unmet need for palliative care

Worldwide, it is estimated that more than 20 million people need palliative care at the end of life each year. Only about 14% of people in need of palliative care currently receive it, approximately 3 million people, mostly in high-income countries. 78% of the unmet need for palliative care is in low-income and middle-income countries.[1]

It has been recently reported that only 20 countries worldwide -of 234 countries, territories and areas studied- have palliative care well integrated into their health-care systems (Australia, Austria, Belgium, Canada, France, Germany, Hong Kong Special Administrative Region, Iceland, Ireland, Italy, Japan, Norway, Poland, Romania, Singapore, Sweden, Switzerland, Uganda, United Kingdom and United States of America), 42% have no palliative care services at all and a further 32% have only isolated palliative care services.[2]

The number of people requiring palliative care rises to at least 40 million if all those that could benefit from palliative care at an earlier stage of their illness are included. This number increases at least double if support to family members is also encompassed.[3]

Palliative care is required for a wide range of diseases. The majority of adults in need of palliative care have chronic diseases such as cardiovascular diseases (39%), cancer (34%), chronic respiratory diseases (10%) and AIDS (6%), among other life-threatening diseases as kidney failure, chronic liver disease, neurological disease or dementia.[3 4]

Despite only about one third of those having chronic diseases needing palliative care suffer from cancer, in most countries, palliative care is mainly aimed at patients with terminal cancer in institutional settings.[5] Hospice is underutilized

for patients with non-malignant yet life-threatening diseases[6 7] and they are under-registered in primary care for palliative care before they die.[8] Nevertheless, there is strong evidence of unmet need for symptom control, psychosocial and family support, informed and open communication and choice at end of life among people with life-threatening non-malignant disease.[9 10 11 12]

It is foreseen an increased need for palliative care with increasing ageing populations and the inexorable rise of chronic diseases worldwide,[13] with their attendant burden of need, demands of care, and use of resources.[14 15 16 17]

Strengthening of palliative care as a component of comprehensive care throughout the life course

In order to satisfy this unmet need for palliative care worldwide, the first ever global resolution on palliative care was launched by the World Health Assembly in 2014.[18]

Palliative care has been defined as an approach that improves the quality of life of patients (adults and children) and their families who are facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and correct assessment and treatment of pain and other problems, whether physical, psychosocial or spiritual. It has been acknowledged that alleviation of suffering is an ethical responsibility of health systems and an ethical duty of health care professionals.

Palliative care, when indicated, is considered to be fundamental to improving the quality of life, well-being, comfort and human dignity for individuals. Inadequate integration of palliative care into health and social care systems is considered to be a major contributing factor to the lack of equitable access to such care.

WHO and Members States have been urged to develop, strengthen and implement, where appropriate, palliative care policies to support the comprehensive strengthening of health systems to integrate evidence-based, cost-

effective and equitable palliative care services in the continuum of care, across all levels, with emphasis on primary care, community and home-based care, and universal coverage schemes.

End of life, end of life transitions and early palliative care

There is a lack of clear definition for several concepts regarding end of life care, which include, among others terns, ñend of lifeò itself (different survival durations are considered for this period, ranging from less than 24 months to days) and ñtransition of careò.[19]

Despite de paucity of references in the literature aimed at conceptualizing or defining ñend of lifeò and ñtransition of careò, a preliminary conceptual framework to help build standardized consensual definitions have been recently developed (Figure 1). End of life, sharing similar meaning with terminally ill and terminal care, has been defined as progressive life-limiting disease with a prognosis of months or less. Transition of care has been defined as evolving place, level and goals of care.[20]

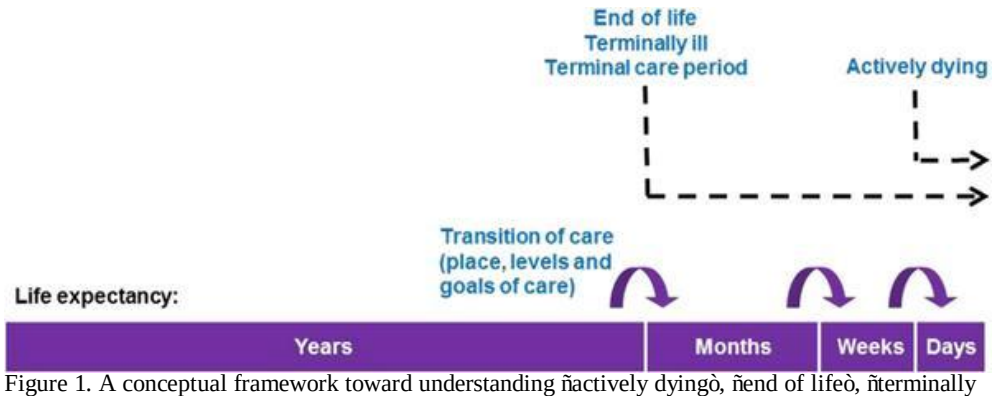

Figure 1. A conceptual framework toward understanding ñactively dyingò, ñend of lifeò, ñterminally illò, ñterminal careò and ñtransition of careò. Hui D et al. J Pain Symptom Manage 2014;47(1): 77ï 89.

In recent years, two different end of life transitions have been proposed[21] (Figure 2): a) transition 1, recognising the period referred to as end of life; and b) transition 2, recognising the period, days or some week, preceding imminent death.

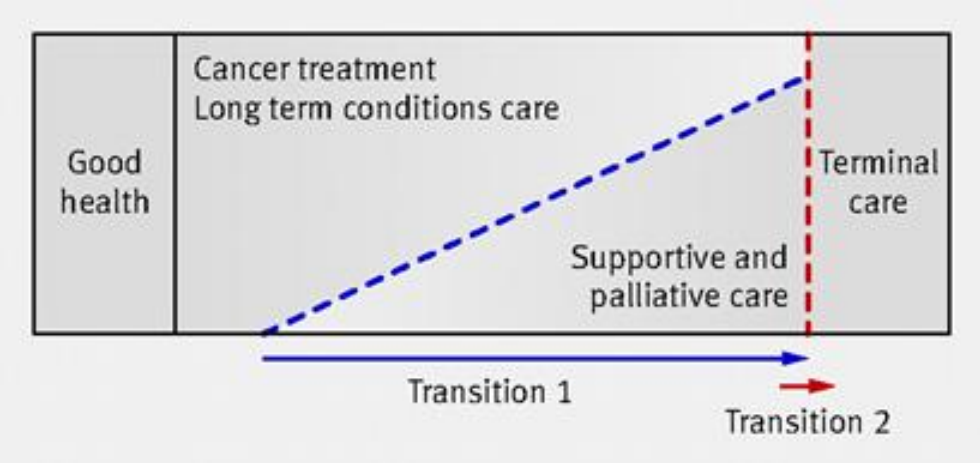

Figure 2. Key phases in end of life care. Boyd K et al. BMJ 2010;341:c4863

Despite there is an urgent need to develop consensus definitions for terms regarding end of life care, palliative care delivered in period after recognition of transition 1 might be identified as early palliative care whereas palliative care delivered in period after recognition of transition 2 might be identified as traditional palliative care. [22 23]

Effectiveness of early palliative care

Palliative care may be most effective when considered early in the course of the illness. Studies in patients with advanced cancer show that early provision of specialty palliative care improves quality of life, lowers spending, and helps clarify treatment preferences and goals of care. Patients who access earlier

specialty palliative care have better clinical outcomes at potentially lower costs.[24] [25] [26] [27] [28]

Although death is not necessarily a high cost event in itself, analysis has shown the last year of life to be characterised by high healthcare costs and therefore of great significance to health providers and insurers.[29]

Translating available evidence into health systems to deliver early palliative care to all people with advanced chronic conditions different than cancer in any setting of care might improve clinical outcomes decreasing costs of care in this population. [22] [30] [31] [32] [33]

End of life trajectories and early palliative care

Trajectories of functional decline at the end of life are quite variable and has been determined to differ among 3 types of illness trajectories (Figure 3): a) cancer death: with steady progression, where advanced incurable illness can, in general, be identified and, usually, a clear terminal phase, allowing performance of activities of daily living until quite late; b) death from organ failure: with gradual decline, punctuated by episodes of acute deterioration and some recovery, with more sudden, seemingly unexpected death, which takes place when the severity of the exacerbation and the patientôs dwindling reserves eventually intersect; and c) dementia/frailty: with prolonged functional dwindling and gradual decline, being needed long-term help with the activities of daily living.[34] [35] [36] Nevertheless, these models have not been confirmed by research and recent findings do question the existence of a predictable pattern of disability in the last year of life based on the condition leading to death, except for advanced dementia.[37]

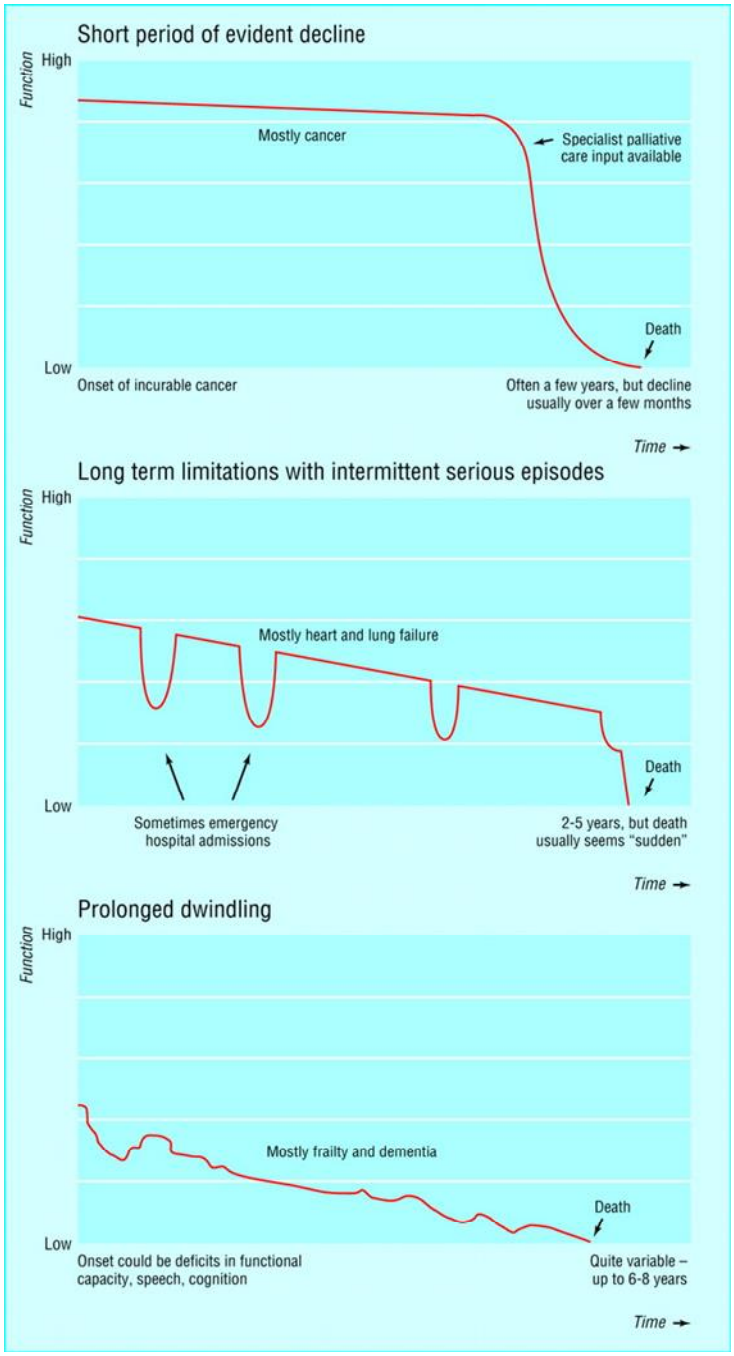

Figure. 3. Typical illness trajectories for people with progressive chronic illness. Adapted from Lynn and Adamson (Lynn J, Adamson DM: Living well at the end of life. Adapting health care to serious chronic illness in old age. Washington: RAND health; 2003) Murray SA et al. BMJ 2005;330:1007-1011.

Identification of people with advanced chronic conditions when they are starting to need a change in place, levels and goals of care, that is recognising transition 1 whatever which end of life trajectory is followed, may have important implications for the organization and delivery of care at the end of life, enabling early palliative care intervention and anticipatory palliative care planning. Nevertheless, for none of these trajectories the right moment to start palliative care -for which early identification is a prerequisite- has been defined yet, particularly regarding patients with non-malignant diseases (Figure 4).[38] It has not been identified any validated tool that could predict the optimal timing to initiate palliative care services.[39]

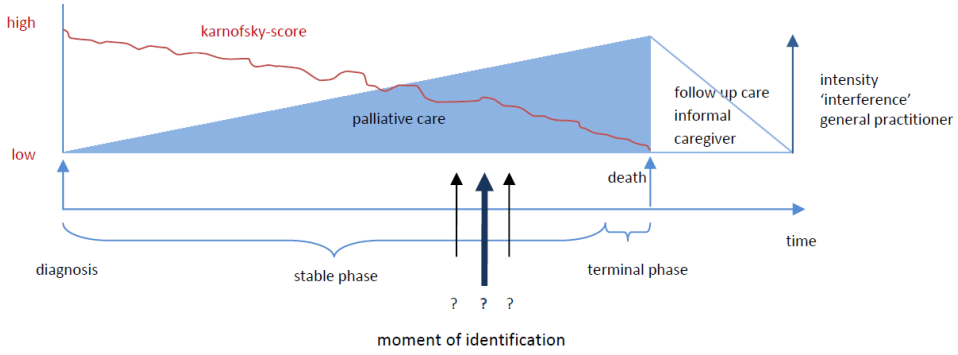

Figure 4. What is the moment to start palliative care? A modified figure of Lynn and Adamson (Lynn J, Adamson DM: Living well at the end of life. Adapting health care to serious chronic illness in old age. Washington: RAND health; 2003) Thoonsen B et al. *BMC Family Practice* 2011, **12**:123

Prognostication in advanced chronic conditions

Prognostication -the process of addressing ñwhat to expectò for an individual's disease course- is essential for meaningful decision-making and end of life planning in advanced illness.[40] The goal of estimating prognosis is to improve clinical decision making and, ultimately, patient outcomes. Clinical decisions are not fully informed unless the patientôs prognosis is considered.[41]

However, prognostication is a greater challenge in non-malignant disease.[42] Compared with cancer, which shows a pattern of decline monophasic and easier to anticipate, determining prognosis is more complicated in life-threatening non-malignant disease. Most of these diseases have ócentryï re-entryô death trajectories, involving episodic, acute exacerbations, frequent hospitalisation, stabilisation and steady decline, making determination of palliative status and referral to palliative care more problematic.[43 44]

Clinicianôs temporal prediction is not a very reliable or robust method of predicting survival. Cliniciansô estimates, even in cancer patients, are inaccurate, over-optimistic and affected by factors such as training, experience, seniority, and level of acquaintance with the patient.[45 46] Prediction rules have been shown to outperform clinicians in terms of prognostication,[47 48] whereas human prediction on its own is fraught with bias.[49] Consequently, clinicians may find prognostic models that attempt to estimate survival useful to help inform their clinical judgment.

Specific tools have been developed to aid clinicians estimate survival in both cancer patients[50 51 52] and non-cancer patients and, among these, from perspectives of disease-specific prognostic models[53 54 55] and generic prognostic models.[56 57]

Prognostic models that have attempted to estimate survival of Ò6 months in non-cancer patients have shown generally poor discrimination, reflecting the less predictable nature of most non-malignant disease.[58]

A systematic review to describe the quality and limitations of validated nonï disease-specific prognostic indices that predict absolute risk of all-cause mortality in older adults has been recently performed.[59] Perspective of disease-specific prognostic models is refused, arguing that older adults are more likely to have more than one chronic illness, as multimorbidity becomes progressively more common with age,[60 61 62] challenging the single-disease framework by which most health care, and medical research and education is configured.[14] Several validated

non-disease-specific prognostic indices for predicting overall mortality -from 6 months to 5 years- for older adults in different clinical settings -community,[63 64 65 66 67 68] nursing home[69 70] and hospital-[71 72 73 74 75 76 57 77] have been identified. Nevertheless, concerns regarding their quality -validation by investigators not involved in studiesô development (only 2 indices), prospective validation in large diverse sample (none), presentation of confidence intervals for either measures of discrimination and calibration (only 2 indices), presence of potential sources of bias (all) and test of transportability (limited)- and limitations -requirement of information that may not be routinely assessed in elderly patients or relying on clinical information from administrative data set (insufficiently accurate), not suited to clinical use and the current existence of updated versions, with changed or no longer present variables, since the development of indices- have been pointed out.

The indicesô ability to better target interventions and improve clinical outcomes, the ultimate goal of estimating prognosis, has not been proved yet. Research into diagnostic tests is scant. Awareness of the need for evidence based diagnostic testing must be increased as valid evidence is necessary before introducing a diagnostic test in clinical practice.[78] This evidence should come from large prospective trials that randomize clinicians to using the index or not, evaluating the effect of the index on prognostic estimates, clinical decision making and patient outcomes. Such large randomized trials have not been performed. Therefore, there is insufficient evidence at this time to recommend the widespread use of prognostic indices in clinical practice[59] and, consequently, an alternative approach to those based on prognostic tools to identify people approaching end of life is needed.

Pragmatic approach to identify people nearing end of life

End of life care and palliative care might not be bounded by a specific prognosis; rather, it might involve the recognition of the irreversibility of a life-limiting medical condition that will likely result in death.[79]

Specialist palliative care is one component of palliative care service delivery and should be available to people in any care setting who need additional expertise, as a resource to support ongoing care by other clinical teams.[80] [30] [31] To optimise quality of life for patients with life-threatening disease, palliative care should run in parallel with potentially curative or disease-modifying treatment.[81] [82]

But, in view of the unmet need for palliative care and the increasing numbers of people who could benefit, a sustainable, quality and accessible palliative care system should be integrated into primary health care, community and home-based care, and hospital care, encompassing a public health approach.[18] [3]

Acknowledging limitations of prognostic indices and predictive models, a pragmatic approach to identify candidates for palliative care needs assessment in primary and secondary care, advocating a person centred approach based not on diagnosis or prognosis, but on the needs of patients and carers in all settings of care -home, care home, and hospital- has been proposed.[21] This pragmatic approach underpins the end of life care strategies that have been implemented in some countries to improving end of life care delivered by primary care teams, hospital staff, and social care services.[83] [84] [85]

According to this pragmatic approach, recognising transition 2, that is to say, identifying patients who are likely to die within days or some week, the period preceding imminent death, might be done using indicators for terminal care based on clinical judgement after careful assessment in all care settings. Recognising transition 2 is considered a core clinical skill, as some core elements of palliative care should be routine aspects of care delivered by any healthcare professional.[30]

Recognising transition 1 by healthcare professional in both primary and secondary care, that is to say, identifying patients who are likely approaching end of life, might be done a) asking themselves what has come to be called as the ñsurprise questionò, updated from its initial version:[81] ñWould you be surprised if this patient were to die in the next 12 months?ò. If the answer is no, then b) using readily identifiable prognostic indicators based on the clinical features of different

advanced illnesses,[34 86 87] updated and complemented with those that have been proved to be reliable indicators of end of life situation,[88] and clinical judgment.

This pragmatic approach for recognising transition 1, based on asking the surprise question and looking for one or more clinical indicators that would suggest a person might be at risk of deteriorating and dying and should be assessed for unmet needs, is the basis of most of the set of identification indicators, conceived as a tools or structured methods, which have been developed in recent years to identifying individuals with palliative care needs,[89] as the Prognostic Indicator Guidance (PIG) of the UK-based Gold Standard Framework (GSF)[90], the Supportive and Palliative Care Indicators Tool (SPICT) in Scotland,[21] the Radboud indicators for Palliative Care needs (RADPAC) in the Netherlands,[91] and the NECPAL CCOMS-ICO© tool in Catalonia, Spain,[92] among others. [93 94 95]

All these tools have been developed to be used in primary care; however, SPICT, PIG and NECPAL CCOMS-ICO© tools are currently also being used in hospital settings and nursing homes.[96 97 98 99 89]

It has been generally assumed that individuals which have been positively identified using any of these available tools do have indeed palliative care needs. It is important to point out that this conclusion cannot be reached directly, as their predictive validity for unmet palliative care needs has not been evaluated yet.[89] Thus, expressions as ñindividuals likely in need of palliative careò or ñindividuals who may benefit from an early palliative care approachò would result more appropriate.

The NECPAL CCOMS-ICO© tool

A comprehensive palliative care programme has been implemented in Catalonia since 1990.[100] Last efficacy assessment performed identified a) considerable

variation in uptake of care facilities by patients with advanced life-threatening non-malignant diseases; b) a need to embed a palliative care approach into conventional services in all settings of the National Health Service (NHS), especially in the community; and c) substantial variation of coverage and models between districts.[101]

To address these challenges, a comprehensive programme has been designed and implemented jointly by the WHO Collaborating Centre for Public Health Palliative Care Programs and the Catalan Department of Health.[102] [85] It is in this context, and as a first measure, that the NECPAL CCOMS-ICO© tool was developed.

The NECPAL CCOMS-ICO© tool is derived from the PIG combined with a further literature review and expert consensus. It has been content-validated in the clinical and cultural contexts of Spain and Catalonia.[92]

Most prognostic and screening tools for people with advanced chronic conditions who may benefit from a palliative care approach have been progressively incorporating general indicators from different domains (functional, nutritional and cognitive status; emotional problems, geriatric syndromes, social vulnerability and others) with solid death predictive values that have been proven to be reliable indicators of end of life situation.[88]

Compared with similar existing tools,[90] [21] [91] [93] [94] [95] the NECPAL CCOMS-ICO© tool (Figures 5-8) is strengthened by containing psychological domain, geriatric syndromes, and any progression of functional and nutritional decline as prognostic indicators. Furthermore, geriatric syndromes and concepts of severity and progression in clinical assessment of toolôs indicators are considered determinant domains in identifying advanced severe frailty, contemplated in the NECPAL CCOMS-ICO© tool as a general and transversal predictor of mortality. Additionally, it is also the only such tool which integrated the request of the patient or family for palliative approach, that is to say patient or carer expressed need, as a trigger to identify individuals in need of palliative care.

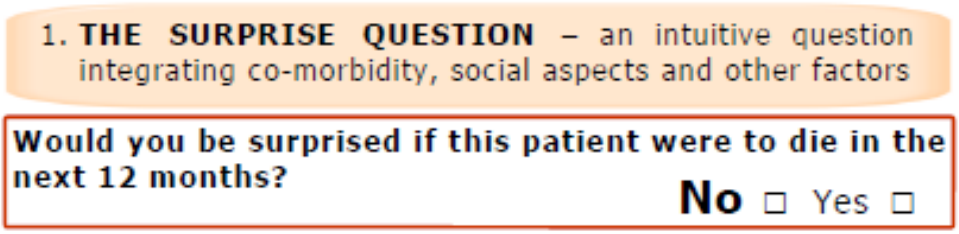

Figure 5. The NECPAL CCOMS-ICO© tool (clinical version). Category 1: the Surprise Question.

Figure 6. The NECPAL CCOMS-ICO© tool (clinical version). Category 2: choice/request or need for palliative care approach.

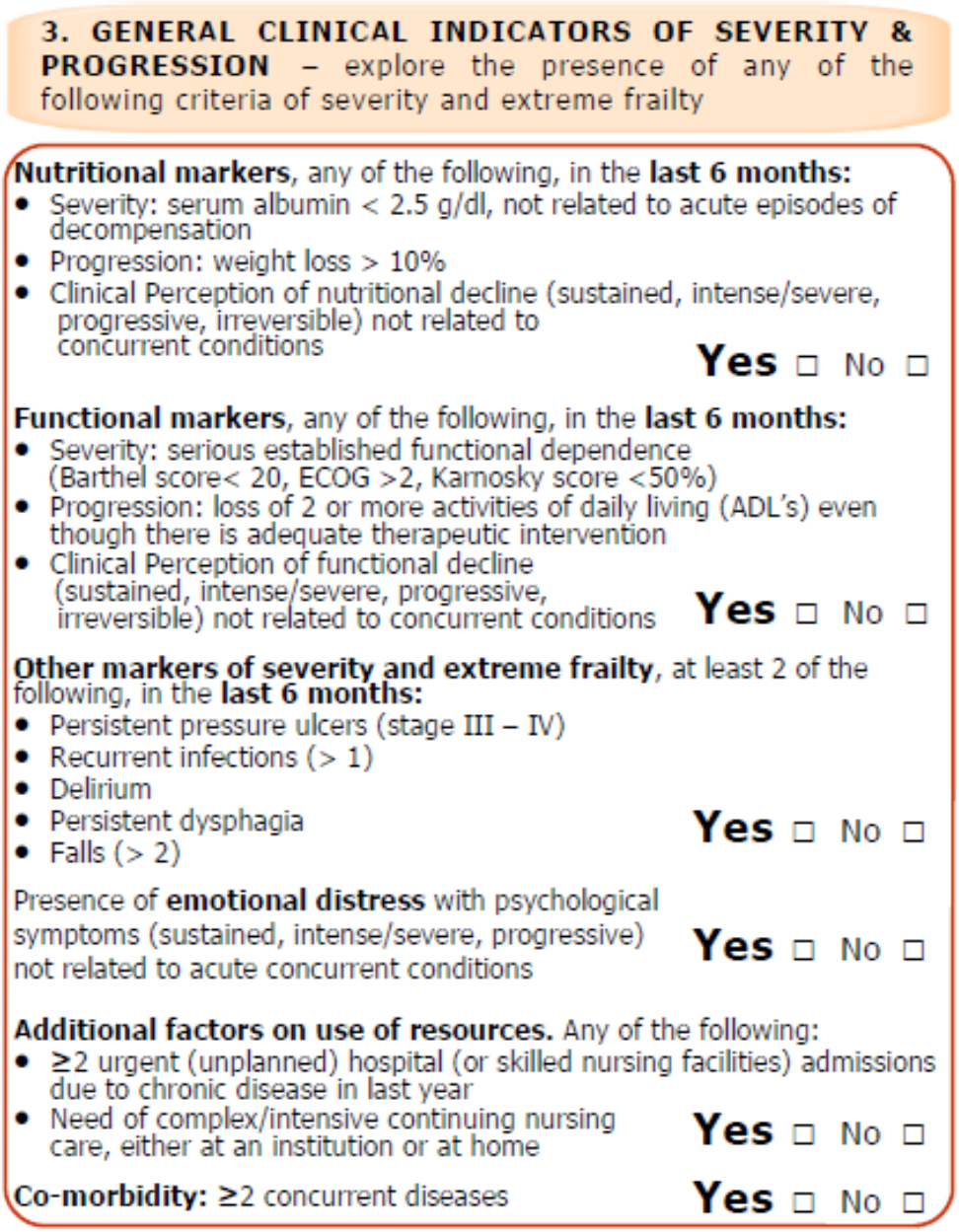

Figure 7. The NECPAL CCOMS-ICO© tool (clinical version). Category 3: general clinical indicators of severity and progression.

4. SPECIFIC CLINICAL INDICATORS OF SEVERITY & PROGRESSION PER DISEASES – explore the presence of specific bad prognosis criteria for the following selected diseases

CANCER (it requires the presence of **one single criterion**)

- Patients with confirmed diagnosis of metastatic cancer (stage IV; and also stage III in some cases –e.g. lung, pancreas, stomach and oesophagus cancers) who present low response or contraindication of specific treatment, progressive outbreak during treatment or metastatic affectation of vital organs (CNS, liver, severe pulmonary disease, etc.)
- Significant functional deteriorating (Palliative Performance Status (PPS) < 50%)
- Persistent, troublesome symptoms, despite optimal treatment of underlying conditions

Yes ☐ No ☐

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) (presence of **two or more** of the following criteria)

- Breathlessness at rest or on minimal exertion between exacerbations
- Difficult physical or psychological symptoms despite optimal tolerated therapy
- In case of having functional respiratory tests (with caveats about quality of testing), disease assessed to be severe: FEV1 <30% or criteria of restricted severe deficit: CVF < 40% / DLCO < 40%
- In case of having arterial blood gases (ABG), accomplishment of oxygen therapy at home criteria or such treatment underway
- Symptomatic heart failure
- Recurrent hospital admissions (> 3 admissions in 12 months due to exacerbations of EPOC)

Yes ☐ No ☐

CHRONIC HEART DISEASE (presence of **two or more** of the following criteria)

- Heart failure NYHA stage III or IV, severe valve disease or inoperable coronary artery disease
- Shortness of breath at rest or minimal exertion
- Difficult physical or psychological symptoms despite optimal tolerated
- In case of having echocardiography: ejection fraction severely affected (< 30%) or severe pulmonary hypertension (Pulmonary pressure > 60 mmHg)
- Renal failure (FG < 30 l/min)
- Repeated hospital admissions with symptoms of heart failure /ischemic heart disease (> 3 last year)

Yes ☐ No ☐

CHRONIC NEUROLOGICAL DISEASES (1): CVA (it requires the presence of **one single criterion**)

- During acute and sub acute phases (< 3 months post-stroke): persistent vegetative or minimal conscious state > 3 days
- During the chronic phase (> 3 months post-stroke): repeated medical complications (aspiration pneumonia despite dysphagia prevention), pyelonephritis (>1), recurrent febrile episodes a despite antibiotics (persistent temperature post > 1 week of antibiotics), pressure ulcers stage 3-4 or dementia with severe criteria post-stroke

Yes ☐ No ☐

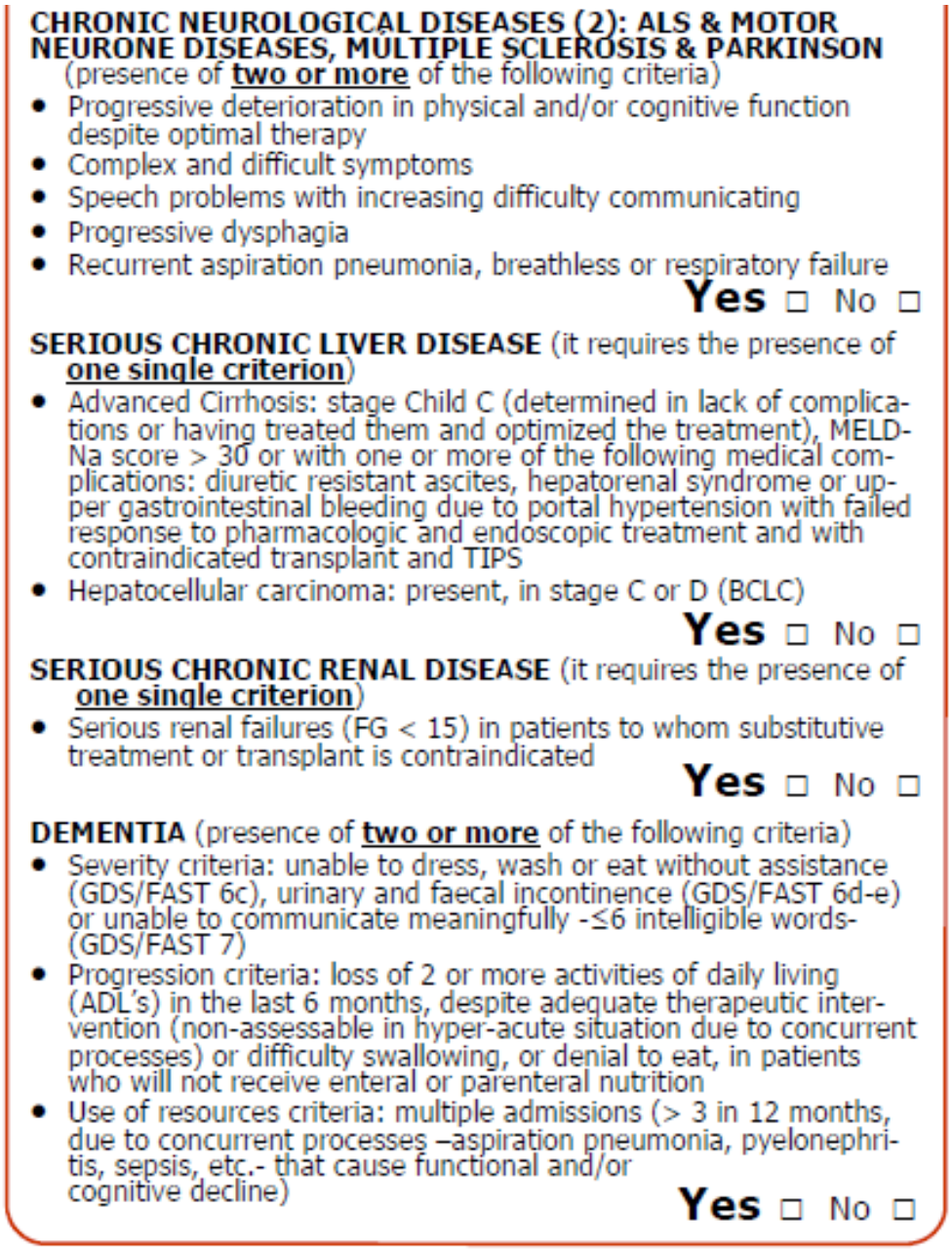

Figure 8. The NECPAL CCOMS-ICO© tool (clinical version). Category 4: disease-specific indicators of severity and progression.

Population-based needs assessment for palliative care

In high income countries, around 75% of the population will die due to chronic conditions, with the ratio of cancer to non-cancer of about 1:2.[103]

The first step in delivering appropriate palliative care is to identify prospectively those individuals within a given population who require such care, becoming essential in generating public health oriented palliative care planning. To date, population-based needs assessment for palliative care has been retrospectively estimated by examining cause of death data or employing estimations. [104] [105] [106] [107] [108] [109] [110] [111]

Although the available tools to identify individuals who may benefit from an early palliative care approach[90] [21] [91] [92] [93] [94] [95] have been developed with the aim to identify those individuals who may require such care, to the best of our knowledge none of them have been employed as a tool to assess the population-based needs for palliative care through identifying the population-based prevalence of these individuals (*Study I*).

Predictive validity

A person centred approach based not on diagnosis or prognosis, but on the needs of patients and carers in all care settings underpins pragmatic approach for identifying individuals who may benefit from an early palliative care intervention.[21] Nevertheless, prognosis plays a central role in clinical decision making.[41] With ready access to critical prognostic information, healthcare professionals will be better equipped to make clinical decisions that are aligned with their patientsô values, preferences, and goals of care.[112] Moreover, patients say that understanding prognosis is important for making life choices, such as engaging in financial planning, arranging custodial care, and deciding when itôs important for long-distance family members to visit.[113] Palliative needs and prognosis are both core aspects of end of life care.

The predictive validity for mortality of available tools to identify individuals who may benefit from an early palliative care approach has received scant attention, in large part because the primary aim of these tools is not to predict mortality, but rather to identify patients with unmet palliative care needs. Although these tools have good face validity, none of them have been validated neither to predict unmet palliative care needs nor to predict mortality. There are insufficient data on their sensitivity, specificity and predictive values with a need for evidence to inform their usefulness.[89]

Although the available tools to identify individuals who may benefit from an early palliative care approach[90 21 91 92 93 94 95] have been developed with the aim to identify those individuals who may require such care, to the best of our knowledge none of them have been evaluated to determine its predictive validity for mortality to inform their usefulness as screening tool for early palliative care from a population-based perspective (*Study II*).

Predictive models

In the 21st century, much of clinical practice involves caring for patients with advanced, progressive, life limiting illness. Prognosis needs to be restored as a core clinical skill, to optimize the patientôs treatment and planning.[114]

A key challenge now facing health and social services is how to identify individuals who are at high risk of death and for whom, according to available evidence, an early palliative care intervention might reduce suffering and improve quality of life.[24 25 26 27 28] óCase-findingô is the term given to the practice of identifying at-risk patients.[115]

In order for early palliative care intervention to have an impact on health outcomes of people with advanced chronic conditions and, subsequently, on their quality of life and dying, it would be convenient, as a first step, an effective and accurate system of case-finding were developed, with the specific aim of identifying those at risk of death. Simple, well-validated predictive models that

provide clinicians with objective measures of palliative status in patients with advanced chronic conditions are needed.[58 39 59]

Although the available tools to identify individuals who may benefit from an early palliative care approach[90 21 91 92 93 94 95] have been developed with the aim to identify those individuals who may require such care, using readily identifiable generic and disease-specific prognostic indicators which have been proven to be reliable indicators of end of life situation, to the best of our knowledge none of them have been employed to develop an effective and simple predictive model for identifying individuals at high risk of death (*Study III*).

V. Research aims

I. Study I

The primary aim of this study was to determine the population-based prevalence of individuals with advanced chronic conditions who may benefit from an early palliative care approach identified by the NECPAL CCOMS-ICO© tool in a mixed urban-rural district in the north of Barcelona. Additionally, the prevalence was determined per setting of care. The secondary aim was to evaluate the degree of agreement between physicians and nurses in identifying individuals. The tertiary aim was to describe characteristics of identified individuals, according to indicators included in the NECPAL CCOMS-ICO© tool, advanced chronic condition and setting of care.

II. Study II

The primary aim of this study was to evaluate the predictive validity for mortality at 3, 6, 12 and 24 months of the NECPAL CCOMS-ICO© tool to inform usefulness as screening tool for early palliative care in individuals with advanced chronic conditions identified in a mixed urban-rural district in the north of Barcelona. The secondary aim was to evaluate the predictive validity for mortality, in the same time points, of the SQ. The tertiary aim was to compare mortality rates between NECPAL and Surprise Question identification (positive vs negative). Additionally, primary, secondary and tertiary aims were explored per advanced chronic condition and setting of care.

III. Study III

The primary aim of this study was to identify factors that are associated with mortality within 24 months using the indicators included in the NECPAL CCOMS-ICO© tool in individuals with advanced chronic conditions identified in a mixed urban-rural district in the north of Barcelona. The secondary aim was to develop a predictive model for identifying individuals at high risk of death. Additionally, primary and secondary aims were explored per advanced chronic condition and setting of care.

VI. Participants

The County of Osona is 1260 sq. km in areal extent, located north of Barcelona in the Autonomous Region of Catalonia (Spain). It is a mixed urban-rural district with a total population of 156807 inhabitants, 21.4% of whom are >65 years of age. The annual mortality rate is 8.81 per 1000.

It has a complete range of health and social care resources including 11 primary care centres; 1 acute bed hospital of 210 beds; 2 intermediate care centres, which provide rehabilitation, palliative care, long-term care, and dementia facilities; and 22 nursing homes, with a total of 1178 beds. It also has a comprehensive organisational system for geriatric, dementia, palliative and chronic care across all settings formally coordinated and linked by a common computerised information system. Care is publicly funded within the NHS and is free at the point of access. All inhabitants are registered to one of the primary care centres.

The primary care centres of the County were classified as urban, ruralï urban and rural areas. Once stratified, one primary care centre from each stratum was randomly selected by using a lottery system, and invited to participate. Primary care centres selected were, respectively, Vic-Sud (23985 inhabitants), Santa Eugènia de Berga (17529 inhabitants), and Roda de Ter (10081 inhabitants), i.e. 51595 registered inhabitants (32.9% of the Countyôs total population). The rest of settings included in the study were the acute bed hospital of the county (Hospital General de Vic), 4 nursing homes (El Nadal, Vilademany, Can Planolas and LõEsquirol) and 1 intermediate care centre (Hospital de la Santa Creu) serving these primary care centres. All invited settings agreed to participate.

Figure 9. Centres participating in the study.

Case identification was undertaken in the period of November 2010 to October 2011 in a) selected primary care centres, b) all inpatient units of acute bed hospital, c) all inpatient units of intermediate care centre, and d) nursing homes, serving these 3 primary care centres.

We excluded outpatient clinics, adult day care facilities and day hospitals on the assumption that these patients would be identified by their healthcare professionals in primary care centres. Patients admitted to acute bed hospital and intermediate care centre but living in areas served by other primary care centres not included in the study were also excluded, as well as residents in nursing homes living there for less than 1 year and place of residence served by other primary care centres.

Cases were identified by healthcare professionals (physicians and nurses) in each health facility. In primary care centres, a list of patients suffering from advanced chronic conditions was generated using different methods, including primary care clinical risk groups (CRGs),[116 117] home care users and registers, if available, of patients with any of the 10 selected chronic diseases or conditions identified as inclusion criteria in the NECPAL CCOMS-ICO© tool (Figure 10).

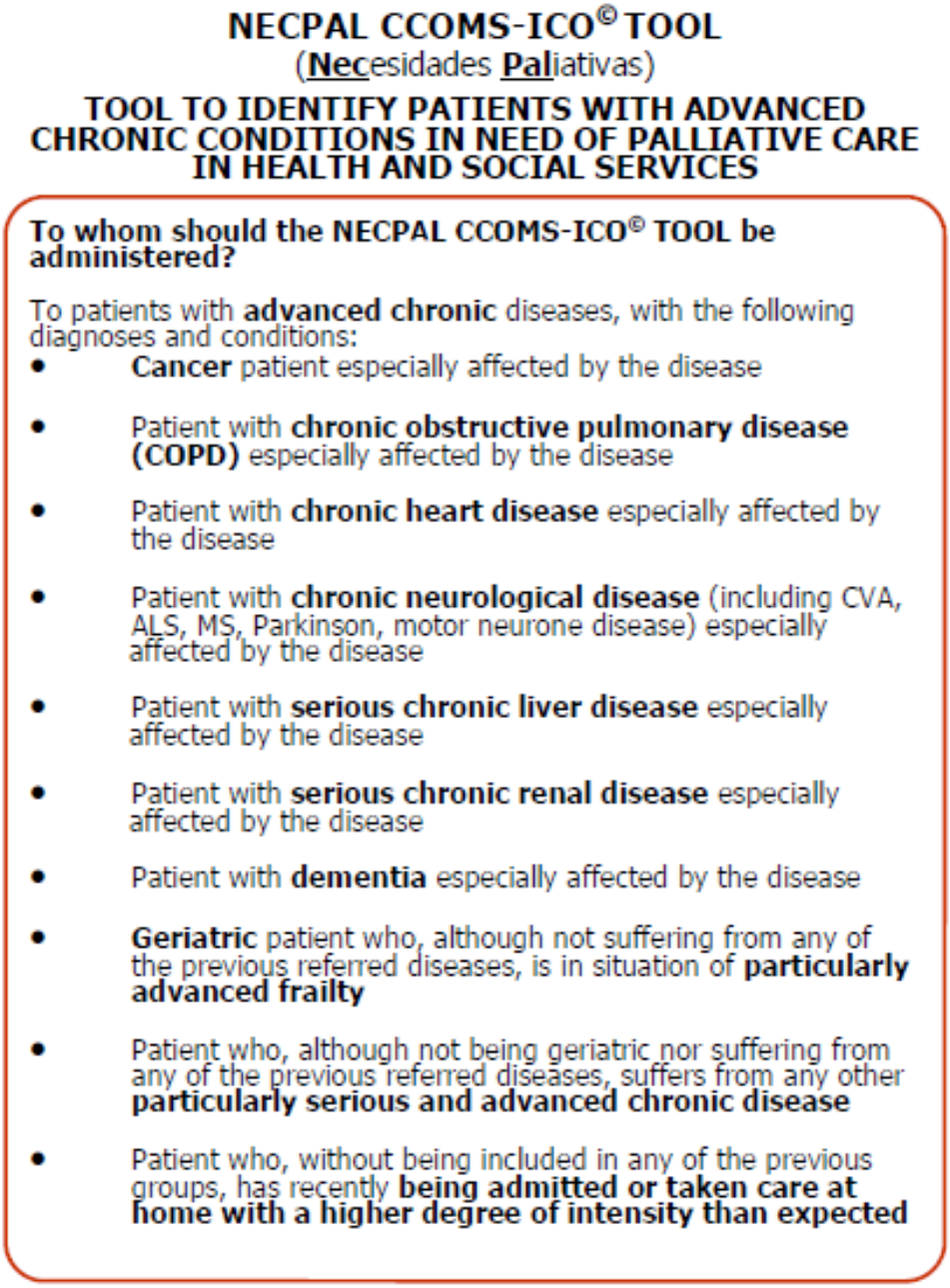

Figure 10. Diseases and conditions included in the NECPAL CCOMS-ICO© tool, identifying to whom should be administered (inclusion criteria).

In inpatient settings, case identification was made from lists of admitted patients. From these lists, physician and nurse were asked to select (individually and,

afterwards, in combination) all possible individuals with advanced chronic conditions to elaborate the final list (cohort recruited). Agreement between physician and nurse was not mandatory for recruitment.

Ethical oversight

This research project was formally approved by the ethical research committees of institutions involved in its execution (2010/PREVOsona: P10/65 and EO65) and patient informed consent was not required on the basis of the routine nature, without specific study-assessments or procedures, of information collected from patientôs clinical records and healthcare professionals.

VII. Methods

I. Study I

Study Design

This is a cross-sectional, population-based study to determine the population-based prevalence of individuals with advanced chronic conditions and palliative care needs identified by the NECPAL CCOMS-ICO© tool in a mixed urban-rural district.

Variables

To determine the population-based prevalence of patients with advanced chronic conditions in need of a palliative care approach, it was employed the Catalan version of the NECPAL CCOMS-ICO© tool,[118] which has the following categories and indicators (study variables):

- Category 1: THE SURPRISE QUESTION
  - Would you be surprised if this patient were to die in the next 12 months?

- Category 2: CHOICE / REQUEST OR NEED
  - Choice / Request: Have either the patient with advanced disease or the main caregiver requested, in explicit or implicit manner, palliative/comfort treatments exclusively? Do they suggest limitation of therapeutic effort or reject specific treatments or those with curative purposes?
  - Need: Do you consider this patient requires palliative care or palliative treatment at this moment?

- Category 3: GENERAL CLINICAL INDICATORS OF SEVERITY & PROGRESSION

a) Nutritional markers, any of the following, in the last 6 months:
   - Clinical perception of nutritional decline (sustained, intense/severe, progressive, irreversible) not related to concurrent conditions
   - Severity: serum albumin < 2.5 g/dl, not related to acute episodes of decompensation
   - Progression: weight loss > 10%

b) Functional markers, any of the following, in the last 6 months:
   - Clinical perception of functional decline (sustained, intense/severe, progressive, irreversible) not related to concurrent conditions
   - Severity: serious established functional dependence (Barthel score< 20, ECOG >2, Karnosky score <50%)
   - Progression: loss of 2 or more activities of daily living (ADLôs) even though there is adequate therapeutic intervention

c) Other markers of severity and extreme frailty, at least 2 of the following, in the last 6 months:
   - Persistent pressure ulcers (stage III ï IV)
   - Recurrent infections (> 1)
   - Delirium
   - Persistent dysphagia
   - Falls (> 2)

d) Presence of emotional distress with psychological symptoms (sustained, intense/severe, progressive) not related to acute concurrent conditions

e) Additional factors on use of resources. Any of the following:
   - urgent (unplanned) hospital (or skilled nursing facilities) admissions due to chronic disease in last year
   - Need of complex/intensive continuing nursing care, either at an institution or at home

f) Co-morbidity: Charlson index

- Category 4: SPECIFIC CLINICAL INDICATORS OF SEVERITY & PROGRESSION PER DISEASES

a) CANCER (it requires the presence of one single criterion):
   - Patients with confirmed diagnosis of metastatic cancer (stage IV; and also stage III in some cases ï e.g. lung, pancreas, stomach and oesophagus cancers) who present low response or contraindication of specific treatment, progressive outbreak during treatment or metastatic affectation of vital organs (CNS, liver, severe pulmonary disease, etc.)
   - Significant functional deteriorating (Palliative Performance Status (PPS) < 50%)
   - Persistent, troublesome symptoms, despite optimal treatment of underlying conditions

b) CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) (presence of two or more of the following criteria):
   - Breathlessness at rest or on minimal exertion between exacerbations
   - Difficult physical or psychological symptoms despite optimal tolerated therapy
   - In case of having functional respiratory tests (with caveats about quality of testing), disease assessed to be severe: FEV1 <30% or criteria of restricted severe deficit: CVF < 40% / DLCO < 40%
   - In case of having arterial blood gases (ABG), accomplishment of oxygen therapy at home criteria or such treatment underway
   - Symptomatic heart failure
   - Recurrent hospital admissions (> 3 admissions in 12 months due to exacerbations of EPOC)

c) CHRONIC HEART DISEASE (presence of two or more of the following criteria):

- Heart failure NYHA stage III or IV, severe valve disease or inoperable coronary artery disease
- Shortness of breath at rest or minimal exertion
- Difficult physical or psychological symptoms despite optimal tolerated
- In case of having echocardiography: ejection fraction severely affected (< 30%) or severe pulmonary hypertension (Pulmonary pressure > 60 mmHg)
- Renal failure (FG < 30 l/min)
- Repeated hospital admissions with symptoms of heart failure /ischemic heart disease (> 3 last year)

d) CHRONIC NEUROLOGICAL DISEASES (1): CVA (it requires the presence of one single criterion):
   - During acute and sub-acute phases (< 3 months post-stroke): persistent vegetative or minimal conscious state > 3 days
   - During the chronic phase (> 3 months post-stroke): repeated medical complications (aspiration pneumonia despite dysphagia prevention), pyelonephritis (>1), recurrent febrile episodes a despite antibiotics (persistent temperature post > 1 week of antibiotics), pressure ulcers stage 3-4 or dementia with severe criteria post-stroke

e) CHRONIC NEUROLOGICAL DISEASES (2): ALS & MOTOR NEURONE DISEASES, MÚLTIPLE SCLEROSIS & PARKINSON (presence of two or more of the following criteria):
   - Progressive deterioration in physical and/or cognitive function despite optimal therapy
   - Complex and difficult symptoms
   - Speech problems with increasing difficulty communicating
   - Progressive dysphagia
   - Recurrent aspiration pneumonia, breathless or respiratory failure

f) SERIOUS CHRONIC LIVER DISEASE (it requires the presence of one single criterion):
   - Advanced cirrhosis: stage Child C (determined in lack of complications or having treated them and optimized the treatment), MELD-Na score > 30 or with one or more of the following medical complications: diuretic resistant ascites, hepatorenal syndrome or upper gastrointestinal bleeding due to portal hypertension with failed response to pharmacologic and endoscopic treatment and with contraindicated transplant and TIPS
   - Hepatocellular carcinoma: present, in stage C or D (BCLC)

g) SERIOUS CHRONIC RENAL DISEASE (it requires the presence of one single criterion):
   - Serious renal failures (FG < 15) in patients to whom substitutive treatment or transplant is contraindicated

h) DEMENTIA (presence of two or more of the following criteria):
   - Severity criteria: unable to dress, wash or eat without assistance (GDS/FAST 6c), urinary and faecal incontinence (GDS/FAST 6d-e) or unable to communicate meaningfully -Ò6 intelligible words- (GDS/FAST 7)
   - Progression criteria: loss of 2 or more activities of daily living (ADLôs) in the last 6 months, despite adequate therapeutic intervention (non-assessable in hyper-acute situation due to concurrent processes) or difficulty swallowing, or denial to eat, in patients who will not receive enteral or parenteral nutrition
   - Use of resources criteria: multiple admissions (> 3 in 12 months, due to concurrent processes ï aspiration pneumonia, pyelonephritis, sepsis, etc.- that cause functional and/or cognitive decline)

Socio-demographic data, as gender, age and place of residence were also collected. At least one inclusion criteria had to be fulfilled. In case of

multimorbidity, with more than one inclusion criteria fulfilled, the most likely cause of death for such individual had to be identified by physician and was considered the main inclusion criteria.

All individuals from cohort recruited were assessed by employing the NECPAL CCOMS-ICO© tool. Quantitative variables were retrieved, if available, from patientôs clinical records by the investigatorsô team after interview with healthcare professionals (physician and nurse concurrently) to respond to categories 1, 2 and indicators to be answered by clinical judgement in category 3. Category 1, the surprise question, was answered independently by physician and nurse.

We categorised recruited individuals as surprise question positive (SQ+) when, at least, one of the attending healthcare professionalsô answer was ñnoò to the surprise question (i.e. ñI will not be surprised if the patient dies within one yearò). SQ+ individuals were also considered as NECPAL+ when they presented, at least, one positive additional category from among the remaining indicators of the tool, as defined (Figure 11). All individuals classified as NECPAL+ were considered likely in need of palliative care.

The individualsô advanced chronic conditions were categorised according to established end of life trajectories, even though individuals with dementia were analysed separately from those classified as having advanced frailty.

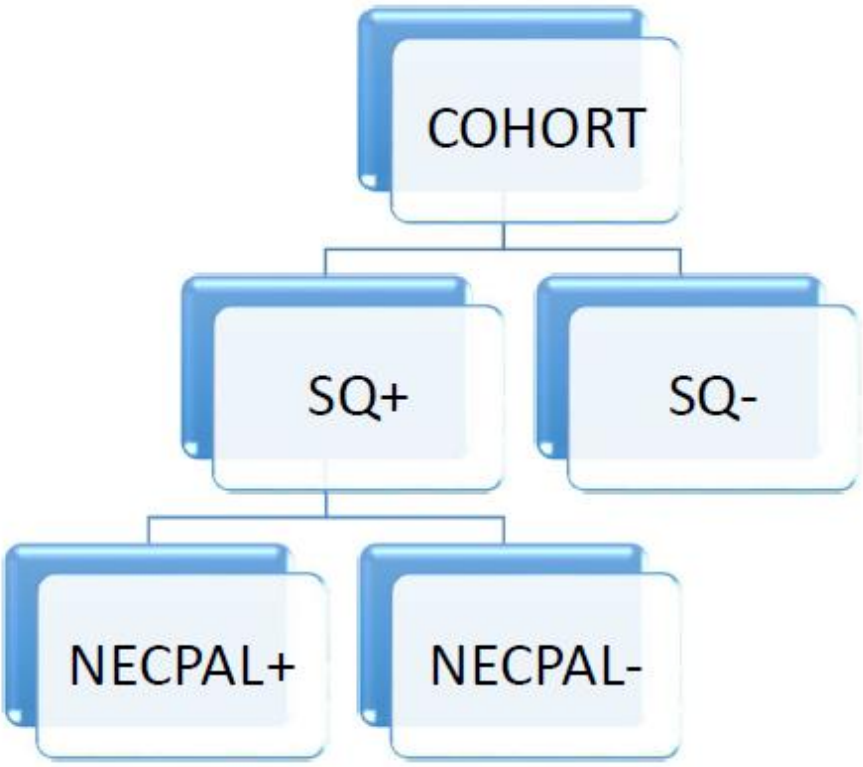

Figure 11. Classification of recruited individuals in three main groups: cohort, SQ+ and NECPAL+.

In order to reduce systematic error, all definitions, procedures and measures were standardized and followed according to the study operations manual; all people involved in collecting data were trained to proceed according to standardized methodology; and collectors of quantitative data were blinded regarding patientsô SQ condition.

Statistical analysis

Population-based prevalence according to 3 main studied groups (cohort, SQ+, NECPAL+ individuals) was calculated based on census data of the County of Osona using the population served by the primary care centres as the denominator.

The numerator included identified individuals in primary care centres and also individuals registered as inpatients at the acute bed hospital, intermediate care centre and nursing homes serving these areas at the time of data collection.

We calculated the specific prevalence within acute bed hospital, intermediate care centre and nursing homes separately using as denominator and numerator the total number of registered and identified individuals present in each setting, respectively, regardless of place of residence. Prevalence per general practitioner in primary care was also calculated.

For global estimates, duplicated cases (individuals identified in more than one setting simultaneously) were assigned, by default, to primary care centres.

Absolute numbers and percentages by age, gender, condition and setting of care were calculated for these 3 main groups of individuals.

Agreement between physicians and nurses in the identification of SQ+ individuals was calculated using Kappa statistic.

The Chi-square test for equality of proportions was used to compare characteristics of identified individuals per advanced chronic condition and setting of care. The Kruskal-Wallis test was used to compare median age values also per advanced chronic condition and setting of care. The results were considered significant at $p<0.05$.

The package used for statistical analyses of the data was STATA v11 for Windows.

II. Study II

Study design

This is a longitudinal, prospective, cohort study to evaluate the predictive validity for mortality at 3, 6, 12 and 24 months of the NECPAL CCOMS-ICO© tool and the SQ as screening tools for early palliative care in individuals with advanced chronic conditions identified in a mixed urban-rural district.

Variables

Based on a chart review, individuals from recruited cohort in previous population-based prevalence study that died during the 2-year study period were identified. To assure comprehensive and accurate mortality data, this information (obtained from patient medical records) was cross-checked with lists provided by the individual health care services, death registries, and hospital and independent care centre registries. Participant mortality status (alive, dead, or lost to follow up) was verified at 3, 6, 12 and 24 months and recorded, as well as date, cause, and place of death.

Statistical analysis

To evaluate predictive validity for mortality, that is to say, to verify the correlation of the two tools (NECPAL and SQ) with individual status at 3 months, 6 months, 1 year and 2 years, both sensitivity (proportion of true positives -individuals deceased and positive identification- among those that did die) and specificity (proportion of true negatives -individuals living and negative identification- among those that were alive) were assessed, as well as positive predictive value (proportion of true positives among those with positive identification) and negative predictive value (proportion of true negatives among those with negative

identification). The binomial proportion confidence intervals for these measures were computed using a normal approximation.

The Chi-square test for equality of proportions was used to compare mortality rates at 3, 6, 12 and 24 months (the Fisher Exact Probability test was used when some expected cell frequencies were lower than 5). The results were considered significant at $p<0.05$.

The nonparametric survival curve estimation was performed using the Kaplan-Meier method. The Log-rank test was used to determine differences between survival curves.

The risk ratio was calculated to compare risk of death among positive and negative identification groups for both tools (NECPAL and SQ) at 3, 6, 12 and 24 months.

Variables analysed included advanced chronic condition, setting of care, gender and age.

All statistical analyses were implemented using the SPSS and the R packages.

III. Study III

Study design

This is a longitudinal, prospective, cohort study to identify factors that are associated with mortality within 24 months using the indicators included in the NECPAL CCOMS-ICO© tool in individuals with advanced chronic conditions identified in a mixed urban-rural district to develop a predictive model for identifying individuals at high risk of death.

Variables

Indicators included in the NECPAL CCOMS-ICO© tool and mortality status at 3, 6, 12 and 24 months were analysed in the whole cohort of individuals recruited in previous population-based prevalence study. Collection of information has been described previously in studies I and II, respectively.

Statistical analysis

A semi-parametric Cox proportional regression analysis was used to identify indicators included in the NECPAL CCOMS-ICO© tool associated with mortality within 24 months after identification.

Backward and forward step-wise selection of the best predictive covariates was carried out by using the AIC (Akaike Information Criterion) statistic.

Schoenfeldôs residuals test was used to evaluate the proportionality of hazards in estimated Cox model.

The proposed predictive model was used to identify individuals with an increased risk to die based on the indicators that were significantly associated with death among those included in the NECPAL CCOMS-ICO© tool.

To evaluate the predictive modelôs ability to accurately classify the individuals, sensitivity (proportion of individuals predicted to be deceased among those that did die) and specificity (proportion of individuals predicted to be alive among those that were alive) were calculated. The Receiver Operating Characteristic (ROC) curve, a graphical plot of the sensitivity against specificity of the model for different cut points, and the area under the curve (AUC) were also calculated. The area under the ROC curve is a reflection of how good the estimated model is at discriminating between individuals with a risk to die or to be alive. The greater the area under the curve the better predictive model. The best possible prediction method, also called the perfect classification, should fall at the area in the upper left corner (0, 1) of the ROC space representing 100% sensitivity (no false

negatives) and 100% specificity (no false positives). An AUC equal to 0.5 suggest no discrimination, 0.7 to less than 0.8 being acceptable, 0.8 to 0.9 being excellent, and above 0.9 being outstanding discrimination.[119]

Predictive modelôs ability were additionally studied for estimated Cox models proposed per advanced chronic condition and setting of care.

All statistical analyses were implemented using the R package.

VIII. Results

I. Study I

A total number of 1.063 individuals were recruited as having advanced chronic conditions. Of them, 840 were identified as SQ+. Among these, 783 were also identified as NECPAL+ (Figure 12). Only 57 individuals (6.8%) identified as SQ+ were not NECPAL+.

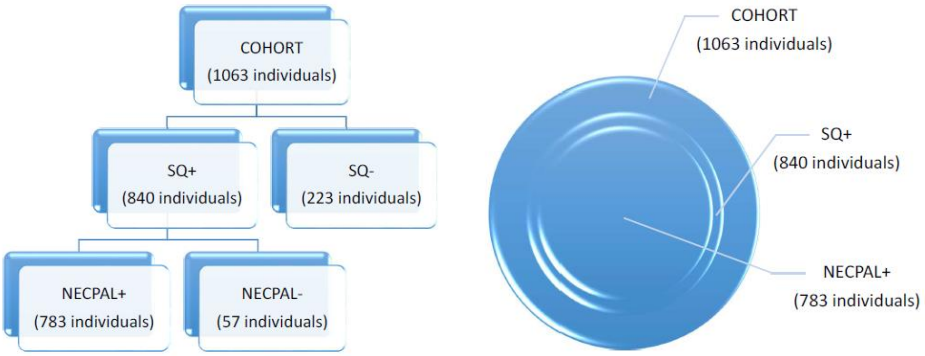

Figure 12. Recruitment of individuals classified in three main groups: cohort, SQ+ and NECPAL+.

Primary care services recruited 68.7% of participant individuals, being the main setting of recruitment for all advanced chronic conditions considered, except for dementia, where the main setting of recruitment were nursing homes, with 55.9% of all recruited individuals suffering from this disease. 38.3% of recruited individuals presented advanced frailty and 32.4%, some kind of organ failure disease, being both the most prevalent advanced chronic conditions (Table 1).

CONDITION n (%) / SETTING n (%)	Cancer	Dementia	Advanced frailty*	Organ failure	Total
Primary care centres	76 (10.4) (70.4)	78 (10.7) (38.2)	325 (44.4) (79.8)	252 (34.5) (73.3)	731 (100.0) (68.7)
Intermediate care centre	17 (23.0) (15.7)	8 (10.8) (3.9)	22 (29.7) (5.4)	27 (36.5) (7.8)	74 (100.0) (7,0)
Acute bed hospital	13 (24.1) (12.0)	4 (7.4) (2.0)	6 (11.1) (1.5)	31 (57.4) (9.0)	54 (100.0) (5.1)
Nursing homes	2 (1.0) (1.9)	114 (55.9) (55.9)	54 (26.5) (13.3)	34 (16.6) (9.9)	204 (100.0) (19.2)
Total	108 (10.1) (100.0)	204 (19.2) (100.0)	407 (38.3) (100.0)	344 (32.4) (100.0)	1063 (100.0) (100.0)

Table 1. Recruitment per advanced chronic condition and setting of care.
* Refers to elderly individuals considered to present advanced frailty (subjectively evaluated by healthcare professionals, without using specific or standardized measures).

Population-based prevalence and prevalence per setting of care

Population-based prevalence of individuals with advanced chronic conditions who may benefit from an early palliative care approach, that is to say NECPAL+ individuals, was 1.5% (Table 2).

Per settings of care, high prevalence were observed in intermediate care centre, nursing homes and acute bed hospital, being of 69.6%, 53.9% and 37.3% respectively. A prevalence of 1% was observed in primary care centres, with a mean of 18 NECPAL+ individuals per general practitioner.

	Population n	COHORT n (%)	SQ+ n (%)	NECPAL+ n (%)
Study population	51595	1063 (2.1)	840 (1.6)	783 (1.5)
Primary care centres	51595	731 (1.4)	557 (1.1)	524 (1.0)
General Practitioner (n=29)	1779*	24.9** (range:16-37)	19.6**	17.8**
Intermediate care centre	92	87 (94.6)	64 (69.6)	64 (69.6)
Acute bed hospital	161	69 (42.9)	67 (41.6)	60 (37.3)
Nursing homes	295	213 (72.2)	182 (61.7)	159 (53.9)

Table 2. Population-based prevalence and prevalence per setting of care of individuals with advanced chronic conditions per group (cohort, SQ+ and NECPAL+).
* Mean population served by each General Practitioner.
** Mean number of recruited, SQ+ and NECPAL+ individuals attended to by each General Practitioner.

The vast majority of individuals with advanced chronic conditions who may benefit from an early palliative care approach were living at home or nursing homes. Among NECPAL+ individuals, almost two thirds were female and the mean age was 81 years old. SQ+ group and NECPAL+ group were equal among individuals with cancer and dementia, as well as among individuals recruited in intermediate care centre and acute bed hospital. The most prevalent conditions among NECPAL+ individuals were organ failure and advanced frailty, followed by dementia. Cancer is the less prevalent disease among individuals with advanced chronic conditions who may benefit from an early palliative care approach, with a ratio cancer/non-cancer of 1/7 (Table 3).

	COHORT (n=1063)	SQ+ (n=840)	NECPAL+ (n= 783)
Age (years); mean (SD)	**80.8 (11.8)**	**81.2 (11.8)**	**80.9 (12.0)**
Gender; n (%)			
Male	**377 (35.5)**	**318 (37.9)**	**302 (38.6)**
Female	**686 (64.5)**	**522 (62.1)**	**481 (61.4)**
Advanced chronic condition; n (%)			
Cancer	**108 (10.1)**	**101 (12.0)**	**101 (12.9)**
Dementia	**204 (19.2)**	**186 (22.1)**	**183 (23.4)**
Advanced frailty	**407 (38.3)**	**285 (34.0)**	**246 (31.4)**
Organ failure	**344 (32.4)**	**268 (31.9)**	**253 (32.3)**
Lung	64 (6.0)	52 (6.2)	51 (6.5)
Heart	85 (8.0)	80 (9.5)	78 (10.0)
Neurological	78 (7.4)	53 (6.3)	47 (6.0)
Liver	16 (1.5)	15 (1.8)	15 (1.9)
Kidney	31 (2.9)	26 (3.1)	24 (3.1)
Other chronic disease	42 (4.0)	25 (3.0)	22 (2.8)
Other	28 (2.6)	17 (2.0)	16 (2.0)
Setting of care; n (%)			
Primary care centres	**731 (68.7)**	**557 (66.4)**	**524 (66.9)**
Intermediate care centre	**74 (7.0)**	**55 (6.5)**	**55 (7.1)**
Acute bed hospital	**54 (5.1)**	**51 (6.1)**	**50 (6.4)**
Nursing homes	**204 (19.2)**	**177 (21.0)**	**154 (19.6)**

Table 3. Population distribution of recruited individuals (cohort, SQ+ and NECPAL+) per age, gender, advanced chronic condition and setting of care.

Degree of agreement between physicians and nurses

There was an agreement of 76.9% of cases between physicians and nurses in the identification of SQ+ individuals, which is a moderate degree of concordance (Kappa=0.4776; p <0.001) (Table 4).

	Nurses			
	n (%)	Yes	No	Total
Physicians	Yes	223 (20.98)	77 (7.24)	300 (28.22)
	No	169 (15.90)	594 (55.88)	763 (71.78)
	Total	392 (36.84)	671 (63.16)	1,063 (100)

Table 4. Agreement between physicians and nurses in the identification of SQ+ individuals.

Characteristics of recruited individuals

Only 21% of recruited individuals were not identified as SQ+.

Among NECPAL+ individuals, choice or demand of palliative care was most frequently requested by carers than by individuals itself, with frequencies of 26.6% and 5.6% respectively. Only 15.5% of NECPAL+ individuals were considered to be in need of palliative care approach by healthcare professionals.

Except for individuals with chronic neurological vascular disease and serious chronic renal disease, indicators of severity and progression were present within the majority of individuals with diseases for which these specific indicators were defined. The groups with high percentages were dementia and cancer, with presence of specific severity and progression indicators in 89.1% and 73.6% of cases, respectively.

The most frequent indicators were, nevertheless, those belonging to category 3 (general clinical indicators of severity and progression) with frequencies reaching 94.4% among NECPAL+ individuals. Co-morbidity, identified by Charlson index Ó2, was present in 71.5% of individuals with advanced chronic conditions and palliative care needs (Table 5).

	COHORT				SQ+				NECPAL+			
	Missing n (%)		n (%)		Missing n (%)		n (%)		Missing n (%)		n (%)	
CATEGORY 1: SURPRISE QUESTION	0		840	79.0	0		840	100	0		783	100
CATEGORY 2: CHOICE/DEMAND OR NEED	0		290	27.3	0		268	31.9	0		268	34.1
Individual's request	4	0.38	51	4.8	4	0.48	44	5.2	4	0.51	44	5.6
Carer's request	5	0.47	224	21.1	5	0.59	209	24.9	5	0.64	209	26.6
PC need identified by healthcare professionals	10	0.93	125	11.7	9	1.07	122	14.5	9	1.15	122	15.5
CATEGORY 3: GENERAL CLINICAL INDICATORS	4	0.38	909	85.4	4	0.48	741	88.1	4	0.51	741	94.4
NUTRITIONAL DECLINE												
Clinical nutritional decline	11	1.03	255	24.0	10	1.19	238	28.3	10	1.27	238	30.3
Serum albumin < 2.5	525	49.3	26	2.4	394	46.9	25	3.0	355	45.2	25	3.2
Weight loss >10%	620	58.3	46	4.3	463	55.1	43	5.1	440	56.1	43	5.5
FUNCTIONAL DECLINE												
Clinical functional decline	6	0.56	391	36.7	6	0.71	346	41.1	6	0.76	346	44.1
Severe dependency (Barthel< 20)	30	2.82	127	11.9	24	2.85	118	14.0	22	2.80	118	15.0
Loss ≥2 ADL	15	1.41	266	25.0	13	1.55	244	29.0	12	1.53	244	31.1
GERIATRIC SYNDROMES												
Pressure sores Grade III-IV	9	0.85	36	3.4	8	0.95	34	4.0	8	1.02	34	4.3
Infections with systemic impact >1	7	0.66	46	4.3	7	0.83	42	5.0	7	0.89	42	5.4
Confusional syndromes	4	0.38	140	13.2	4	0.48	123	14.6	4	0.51	123	15.7
Persistent dysphagia	5	0.47	88	8.3	5	0.59	82	9.8	5	0.64	82	10.4
Falls >2	15	1.41	103	9.7	14	1.64	86	10.2	14	1.78	86	11.0
SEVERE EMOTIONAL DISTRESS	41	3.85	199	18.7	37	4.4	166	19.7	31	3.95	166	21.1
USE OF RESOURCES												
Urgent admissions ≥2	8	0.75	127	11.9	7	0.83	115	13.7	6	0.77	111	14.2
Complex/intensive nursing care needs	35	3.29	181	17.0	31	3.69	147	17.5	29	3.69	147	18.7
CO-MORBIDITY: CHARLSON TEST ≥2	12	1.13	690	64.9	10	1.10	571	68.0	8	1.02	560	71.5
CATEGORY 4: SPECIFIC CHRONIC DISEASE												
Cancer	11	9.32	82	69.5	11	9.91	81	73.0	10	9.09	81	73.6
Lung	12	16.7	50	69.4	12	20	41	68.3	11	19.0	41	70.7
Heart	12	12.1	69	69.7	12	12.9	65	69.9	11	12.2	65	72.2
Neurologic (vascular)	11	23.0	9	18.8	11	30.6	6	16.7	10	33.3	6	20.0
Neurologic (progressive)	11	22	33	66.0	11	29.0	25	65.8	10	27.8	25	69.4
Liver	0		14	51.9	0		13	50.0	0		13	52.0
Kidney	12	27.2	15	34.1	12	30	11	27.5	11	29.7	11	29.7
Dementia	12	5.58	186	86.5	12	6.12	172	87.8	10	5.18	172	89.1

Table 5. Characteristics of recruited individuals according to NECPAL CCOMS-ICO© tool indicators per groups (cohort, SQ+ and NECPAL+).

Significant differences were found regarding age and gender per advanced chronic condition.

Among NECPAL+ individuals, mean age was higher within advanced frailty and dementia groups, 86.1 and 85.1 years, respectively; while was lower within organ failure and cancer groups, 76.0 and 72.8 years, respectively (Kruskal-Wallis chi-squared=150.14, p<2.2e-16) (Table 6 and Figure 13). These significant differences were equally observed among individuals of SQ+ and cohort groups.

Age (years); mean SD)	Cancer	Dementia	Advanced frailty	Organ failure	p value
COHORT	72.9 (14.1)	84.5 (6.8)	85.9 (6.4)	75.1 (14.1)	p < 2.2e-16
SQ+	72.8 (14.0)	85.0 (6.5)	86.5 (6.8)	76.0 (14.0)	p < 2.2e-16
NECPAL+	72.8 (14.0)	85.1 (6.5)	86.1 (7.1)	76.0 (14.1)	p < 2.2e-16

Table 6. Age per advanced chronic condition within main groups (cohort, SQ+ and NECPAL+).

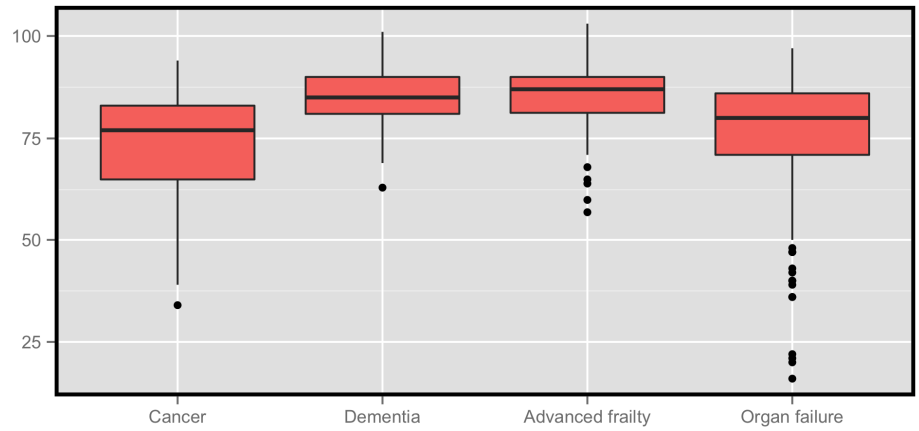

Figure 13. Age per advanced chronic condition within NECPAL+ individuals.

Regarding gender, the majority of individuals likely in need of palliative care within dementia and advanced frailty groups were female, with frequencies of

79.8% and 69.9%, respectively. Male gender was majority within cancer and organ failure groups, although with lower frequencies, of 57.4% and 52.6%, respectively (chi-square=69.58, p<0.0001) (Table 7). These significant differences were equally observed among individuals of SQ+ and cohort groups.

Gender; n (%)	Cancer	Dementia	Advanced frailty	Organ failure	Total	p value
COHORT						
Male	62 (57.4)	40 (19.6)	106 (26.0)	169 (49.1)	377 (35.5)	<0.0001
Female	46 (42.6)	164 (80.4)	301 (74.0)	175 (50.9)	686 (64.5)	
Total	108 (100.0)	204 (100.0)	407 (100.0)	344 (100.0)	1063 (100.0)	
SQ+						
Male	58 (57.4)	37 (19.9)	83 (29.1)	140 (52.2)	318 (37.9)	<0.0001
Female	43 (42.6)	149 (80.1)	202 (70.9)	128 (47.8)	522 (62.1)	
Total	101 (100.0)	186 (100.0)	285 (100.0)	268 (100.0)	840 (100.0)	
NECPAL+						
Male	58 (57.4)	37 (20.2)	74 (30.1)	133 (52.6)	302 (38.6)	<0.0001
Female	43 (42.6)	146 (79.8)	172 (69.9)	120 (47.4)	481 (61.4)	
Total	101 (100.0)	183 (100.0)	246 (100.0)	253 (100.0)	783 (100.0)	

Table 7. Gender per advanced chronic condition within main groups (cohort, SQ+ and NECPAL+).

Finally, significant differences were found regarding age, gender and advanced chronic condition per setting of care.

Among NECPAL+ individuals, mean age was higher within nursing homes, 85.5 years, and lower within primary care centres, intermediate care centre and acute bed hospital, with 80.3, 78.1 and 76.8 years, respectively (Kruskal-Wallis chi-squared=34.26, p=1.74e-07) (Table 8 and Figure 14). These significant differences were equally observed among individuals of SQ+ and cohort groups.

Age (years); mean (SD)	Primary care centres	Intermediate care centre	Acute bed hospital	Nursing homes	p value
COHORT	80.5 (12.3)	76.8 (12.6)	75.6 (12.8)	84.6 (7.3)	p=4.788e-09
SQ+	80.7 (12.7)	78.1 (11.8)	77.0 (11.3)	85.0 (7.3)	p=2.492e-07
NECPAL+	80.3 (12.9)	78.1 (11.8)	76.8 (11.3)	85.2 (6.9)	p=1.746e-07

Table 8. Age per setting of care within main groups (cohort, SQ+ and NECPAL+).

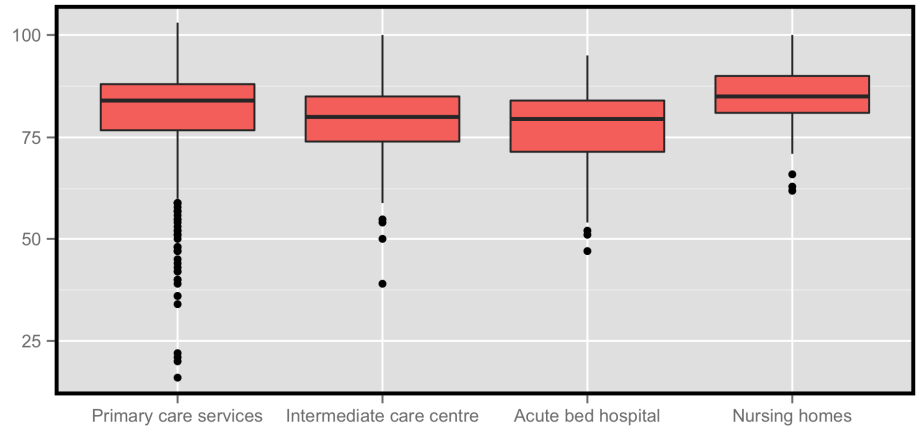

Figure 14. Age per setting of care within NECPAL+ individuals.

Regarding gender, 81.8% of individuals likely in need of palliative care within nursing homes were female, being also majority (58.6%) within primary care services. Male gender was majority within acute bed hospital and intermediate care centre, although with lower frequencies, of 56.0% and 52.7%, respectively (chi-square=39.87, $p<0.0001$) (Table 9). These significant differences were equally observed among individuals of SQ+ and cohort groups.

Gender; n (%)	Primary care centres	Inter-mediate care centre	Acute bed hospital	Nursing homes	Total	p value
COHORT						
Male	274 (37.5)	35 (47.3)	30 (55.6)	38 (18.6)	377 (35.5)	<0.0001
Female	457 (62.5)	39 (52.7)	24 (44.4)	166 (81.4)	686 (64.5)	
Total	731 (100.0)	74 (100.0)	54 (100.0)	204 (100.0)	1063 (100.0)	
SQ+						
Male	228 (40.9)	29 (52.7)	29 (56.9)	32 (18.1)	318 (37.9)	<0.0001
Female	329 (59.1)	26 (47.3)	22 (43.1)	145 (81.9)	522 (62.1)	
Total	557 (100.0)	55 (100.0)	51 (100.0)	177 (100.0)	840 (100.0)	
NECPAL+						
Male	217 (41.4)	29 (52.7)	28 (56.0)	28 (18.2)	302 (38.6)	<0.0001
Female	307 (58.6)	26 (47.3)	22 (44.0)	126 (81.8)	481 (61.4)	
Total	524 (100.0)	55 (100.0)	50 (100.0)	154 (100.0)	783 (100.0)	

Table 9. Gender per setting of care within main groups (cohort, SQ+ and NECPAL+).

Advanced chronic conditions were distributed significantly different among settings of care (Table 10). 69.5% of individuals likely in need of palliative care within nursing homes presented dementia, while within acute bed hospital the majority group (54.0%) was organ failure followed by cancer (26.0%). The most frequent advanced chronic conditions within primary care centres were advanced frailty (38.5%) and organ failure (35.4%) while the most frequent ones within intermediate care centre were organ failure (38.2%) and cancer (27.3%) (chi-square=260.50, $p<0.0001$). These significant differences were equally observed among individuals of SQ+ and cohort groups.

Condition; n (%)	Primary care centres	Inter-mediate care centre	Acute bed hospital	Nursing homes	Total	p value
COHORT						
Cancer	76 (10.4)	17 (23.0)	13 (24.1)	2 (1.0)	108 (10.1)	<0.0001
Dementia	78 (10.7)	8 (10.8)	4 (7.4)	114 (55.9)	204 (19.2)	
Advanced frailty	325 (44.4)	22 (29.7)	6 (11.1)	54 (26.5)	407 (38.3)	
Organ failure	252 (34.5)	27 (36.5)	31 (57.4)	34 (16.6)	344 (32.4)	
Total	731 (100.0)	74 (100.0)	54 (100.0)	204 (100.0)	1063 (100.0)	
SQ+						
Cancer	71 (12.7)	15 (27.3)	13 (25.5)	2 (1.1)	101 (12.0)	<0.0001
Dementia	68 (12.2)	6 (10.9)	4 (7.8)	108 (61.0)	186 (22.2)	
Advanced frailty	226 (40.6)	13 (23.6)	6 (11.8)	40 (22.6)	285 (33.9)	
Organ failure	192 (34.5)	21 (38.2)	28 (54.9)	27 (15.3)	268 (31.9)	
Total	557 (100.0)	55 (100.0)	51 (100.0)	177 (100.0)	840 (100.0)	
NECPAL+						
Cancer	71 (13.5)	15 (27.3)	13 (26.0)	2 (1.3)	101 (12.9)	<0.0001
Dementia	66 (12.6)	6 (10.9)	4 (8.0)	107 (69.5)	183 (23.4)	
Advanced frailty	202 (38.5)	13 (23.6)	6 (12.0)	25 (16.2)	246 (31.4)	
Organ failure	185 (35.4)	21 (38.2)	27 (54.0)	20 (13.0)	253 (32.3)	
Total	524 (100.0)	55 (100.0)	50 (100.0)	154 (100.0)	783 (100.0)	

Table 10. Advanced chronic condition per setting of care within main groups (cohort, SQ+ and NECPAL+).

II. Study II

A total of 1063 individuals were followed up for survival. Excluding 4 missing cases, data was available to assess 1059 (99.6%) of the initial recruited cohort at 24 months. Of these, 837 were SQ+ and 780 were NECPAL+ (Figure 15).

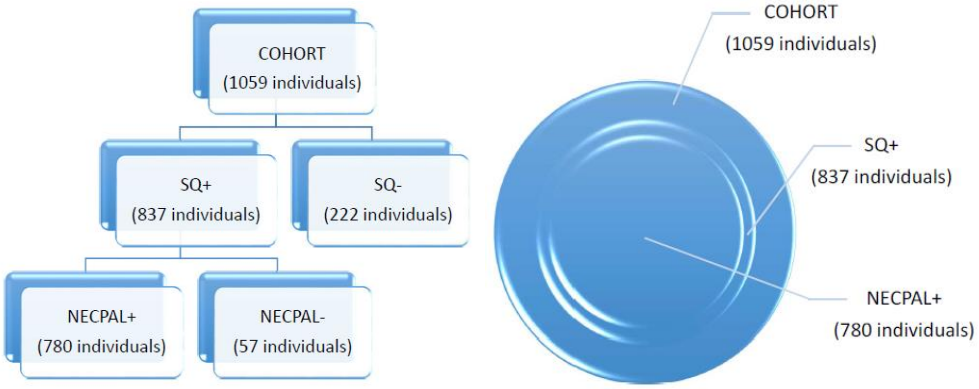

Figure 15. Individuals available for survival analysis classified in three main groups: cohort, SQ+ and NECPAL+.

Mortality rates per main groups

At 3, 6, 12 and 24 months, mortality rates within individuals identified as NECPAL+ were 12.1%, 20.5%, 33.5% and 45.8%, respectively (Table 11).

n and %	COHORT			SQ+			NECPAL+		
	L	D	Total	L	D	Total	L	D	Total
3m	960 (90.7)	99 (9.3)	1059 (100.0)	741 (88.5)	96 (11.5)	837 (100.0)	686 (87.9)	94 (12.1)	780 (100.0)
6m	890 (84.0)	169 (16.0)	1059 (100.0)	673 (80.4)	164 (19.6)	837 (100.0)	620 (79.5)	160 (20.5)	780 (100.0)
12m	773 (73.0)	286 (27.0)	1059 (100.0)	569 (68.0)	268 (32.0)	837 (100.0)	519 (66.5)	261 (33.5)	780 (100.0)
24m	651 (61.5)	408 (38.5)	1059 (100.0)	464 (55.4)	373 (44.6)	837 (100.0)	423 (54.2)	357 (45.8)	780 (100.0)

Table 11. Mortality rates at 3, 6, 12 and 24 months within main groups (cohort, SQ+ and NECPAL+).
L indicates living; D: deceased.

Significant differences in mortality rates were observed per gender, advanced chronic condition and setting of care among NECPAL+ individuals.

Men presented higher mortality rates. At 12 months, the mortality rate for men was 38.1% versus 30.5% for women (chi-square=4.72, p=0.030). A higher mortality rate at 24 months was 50.3% versus 42.9% (chi-square=4.13, p=0.042). These significant differences were equally observed among individuals of SQ+ and cohort groups. No significant differences were observed in mortality rates per gender at 3 or 6 months within any group, except within cohort group at 3 months (Table 12).

	n and %	COHORT				SQ+				NECPAL+			
		L	D	Total	p value	L	D	Total	p value	L	D	Total	p value
3m	Male	332 (88.1)	45 (11.9)	377 (100.0)	p=0.031	273 (85.8)	45 (14.2)	318 (100.0)	p=0.057	257 (85.1)	45 (14.9)	302 (100.0)	p=0.052
	Female	628 (92.1)	54 (7.9)	682 (100.0)		468 (90.2)	51 (9.8)	519 (100)		429 (89.7)	49 (10.3)	478 (100.0)	
	Total	960 (90.7)	99 (9.3)	1059 (100.0)		741 (88.5)	96 (11.5)	837 (100.0)		686 (88.0)	94 (12.0)	780 (100.0)	
6m	Male	306 (81.2)	71 (18.8)	377 (100.0)	p=0.058	249 (78.3)	69 (21.7)	318 (100.0)	p=0.230	234 (77.5)	68 (22.5)	302 (100.0)	p=0.271
	Female	584 (85.6)	98 (14.4)	682 (100.0)		424 (81.7)	95 (18.3)	519 (100.0)		386 (80.8)	92 (19.2)	478 (100.0)	
	Total	890 (84.0)	169 (16.0)	1059 (100.0)		673 (80.4)	164 (19.6)	837 (100.0)		620 (79.5)	160 (20.5)	780 (100.0)	
12m	Male	254 (67.4)	123 (32.6)	377 (100.0)	p=0.002	201 (63.2)	117 (36.8)	318 (100.0)	p=0.021	187 (61.9)	115 (38.1)	302 (100.0)	p=0 .030
	Female	519 (76.1)	163 (23.9)	682 (100.0)		368 (70.9)	151 (29.1)	519 (100.0)		332 (69.5)	146 (30.5)	478 (100.0)	
	Total	773 (73.0)	286 (27.0)	1059 (100.0)		569 (68.0)	268 (32.0)	837 (100.0)		519 (66.5)	261 (33.5)	780 (100.0)	
24m	Male	212 (56.2)	165 (43.8)	377 (100.0)	p=0.009	162 (50.9)	156 (49.1)	318 (100.0)	p=0.041	150 (49.7)	152 (50.3)	302 (100.0)	p=0.042
	Female	439 (64.4)	243 (35.6)	682 (100.0)		302 (58.2)	217 (41.8)	519 (100.0)		273 (57.1)	205 (42.9)	478 (100.0)	
	Total	651 (61.5)	408 (38.5)	1059 (100.0)		464 (55.4)	373 (44.6)	837 (100.0)		423 (54.2)	357 (45.8)	780 (100.0)	

Table 12. Mortality rates per gender at 3, 6, 12 and 24 months within main groups (cohort, SQ+ and NECPAL+).
L indicates living; D: deceased.

Per age, non-significant differences were observed in mortality rates between individuals Ò 75 years and >75 years, neither within any group nor at any time point (Table 13). At 12 months, it was 31.5% versus 34.0%, respectively (chi-square=0.36, p= 0.551). A higher mortality rate at 24 months was 41.2% versus 47.0%, respectively (chi-square=1.75, p= 0.186).

	n and %	COHORT				SQ+				NECPAL+			
		L	D	Total	p value	L	D	Total	p value	L	D	Total	p value
3m	≤75 years	203 (90.2)	22 (9.8)	225 (100.0)	p=0.803	149 (87.1)	22 (12.9)	171 (100.0)	p=0.521	143 (86.7)	22 (13.3)	165 (100.0)	p=0.569
	>75 years	757 (90.8)	77 (9.2)	834 (100.0)		592 (88.9)	74 (11.1)	666 (100.0)		543 (88.3)	72 (11.7)	615 (100.0)	
	Total	960 (90.7)	99 (9.3)	1059 (100.0)		741 (88.5)	96 (11.5)	837 (100.0)		686 (87.9)	94 (12.1)	780 (100.0)	
6m	≤75 years	191 (84.9)	34 (15.1)	225 (100.0)	p=0.696	137 (80.1)	34 (19.9)	171 (100.0)	p=0.915	131 (79.4)	34 (20.6)	165 (100.0)	p=0.973
	>75 years	699 (83.8)	135 (16.2)	834 (100.0)		536 (80.5)	130 (19.5)	666 (100.0)		489 (79.5)	126 (20.5)	615 (100.0)	
	Total	890 (84.0)	169 (16.0)	1059 (100.0)		673 (80.4)	164 (19.6)	837 (100.0)		620 (79.5)	160 (20.5)	780 (100.0)	
12m	≤75 years	170 (75.6)	55 (24.4)	225 (100.0)	p=0.329	118 (69.0)	53 (31.0)	171 (100.0)	p=0.747	113 (68.5)	52 (31.5)	165 (100.0)	p=0.551
	>75 years	603 (72.3)	231 (27.7)	834 (100.0)		451 (67.7)	215 (32.3)	666 (100.0)		406 (66.0)	209 (34.0)	615 (100.0)	
	Total	773 (73.0)	286 (27.0)	1059 (100.0)		569 (68.0)	268 (32.0)	837 (100.0)		519 (66.5)	261 (33.5)	780 (100.0)	
24m	≤75 years	151 (67.1)	74 (32.9)	225 (100.0)	p=0.0502	102 (59.6)	69 (40.4)	171 (100.0)	p=0.214	97 (58.8)	68 (41.2)	165 (100.0)	p=0.186
	>75 years	500 (60.0)	334 (40.0)	834 (100.0)		362 (54.4)	304 (45.6)	666 (100.0)		326 (53.0)	289 (47.0)	615 (100.0)	
	Total	651 (61.5)	408 (38.5)	1059 (100.0)		464 (55.4)	373 (44.6)	837 (100.0)		423 (54.2)	357 (45.8)	780 (100.0)	

Table 13. Mortality rates per age at 3, 6, 12 and 24 months within main groups (cohort, SQ+ and NECPAL+).
L indicates living; D: deceased.

Significant differences were observed in mortality rates per advanced chronic condition among NECPAL+ individuals (Table 14 and Figure 16), with higher mortality rates within cancer and dementia individuals, followed by those within groups of organ failure and advanced frailty, respectively. At 12 months, mortality rates were 64.4% for individuals with cancer, 36.5% in dementia, 30.4% in organ failure, and 21.6% in advanced frailty (chi-square=60.47, p<0.0001). At 24 months, higher mortality rates were 71.3% for individuals with cancer, 56.4% in dementia, 42.7% in organ failure, and 30.6% in advanced frailty (chi-square=58.31, p<0.0001). In most cases (>70%) cause of death was directly related to the principal disease or direct complications thereof. These significant

differences were equally observed among individuals of SQ+ and cohort groups and also at 3 and 6 months within the three main groups.

	n and %	COHORT				SQ+				NECPAL+			
		L	D	Total	p value	L	D	Total	p value	L	D	Total	p value
3m	Cancer	75 (69.4)	33 (30.6)	108 (100.0)	p<.0001	68 (67.3)	33 (32.7)	101 (100.0)	p<.0001	68 (67.3)	33 (32.7)	101 (100.0)	p<.0001
	Dementia	187 (92.6)	15 (7.4)	202 (100.0)		170 (92.4)	14 (7.6)	184 (100.0)		167 (92.3)	14 (7.7)	181 (100.0)	
	Advanced frailty	384 (94.8)	21 (5.2)	405 (100.0)		264 (93.0)	20 (7.0)	284 (100.0)		227 (92.7)	18 (7.3)	245 (100.0)	
	Organ Failure	314 (91.3)	30 (8.7)	344 (100.0)		239 (89.2)	29 (10.8)	268 (100.0)		224 (88.5)	29 (11.5)	253 (100.0)	
	Total	960 (90.7)	99 (9.3)	1059 (100.0)		741 (88.5)	96 (11.5)	837 (100.0)		686 (87.9)	94 (12.1)	780 (100.0)	
6m	Cancer	58 (53.7)	50 (46.3)	108 (100.0)	p<.0001	52 (51.5)	49 (48.5)	101 (100.0)	p<.0001	52 (51.5)	49 (48.5)	101 (100.0)	p<.0001
	Dementia	165 (81.7)	37 (18.3)	202 (100.0)		148 (80.4)	36 (19.6)	184 (100.0)		145 (80.1)	36 (19.9)	181 (100.0)	
	Advanced frailty	366 (90.4)	39 (9.6)	405 (100.0)		247 (87.0)	37 (13.0)	284 (100.0)		212 (86.5)	33 (13.5)	245 (100.0)	
	Organ Failure	301 (87.5)	43 (12.5)	344 (100.0)		226 (84.3)	42 (15.7)	268 (100.0)		211 (83.4)	42 (16.6)	253 (100.0)	
	Total	890 (84.0)	169 (16.0)	1059 (100.0)		673 (80.4)	164 (19.6)	837 (100.0)		620 (79.5)	160 (20.5)	780 (100.0)	
12m	Cancer	41 (38.0)	67 (62.0)	108 (100.0)	p<.0001	36 (35.6)	65 (64.4)	101 (100.0)	p<.0001	36 (35.6)	65 (64.4)	101 (100.0)	p<.0001
	Dementia	133 (65.8)	69 (34.2)	202 (100.0)		118 (64.1)	66 (35.9)	184 (100.0)		115 (63.5)	66 (36.5)	181 (100.0)	
	Advanced frailty	339 (83.7)	66 (16.3)	405 (100.0)		226 (79.6)	58 (20.4)	284 (100.0)		192 (78.4)	53 (21.6)	245 (100.0)	
	Organ Failure	260 (75.6)	84 (24.4)	344 (100.0)		189 (70.5)	79 (29.5)	268 (100.0)		176 (69.6)	77 (30.4)	253 (100.0)	
	Total	773 (73.0)	286 (27.0)	1059 (100.0)		569 (68.0)	268 (32.0)	837 (100.0)		519 (66.5)	261 (33.5)	780 (100.0)	
24m	Cancer	34 (31.5)	74 (68.5)	108 (100.0)	p<.0001	29 (28.7)	72 (71.3)	101 (100.0)	p<.0001	29 (28.7)	72 (71.3)	101 (100.0)	p<.0001
	Dementia	92 (45.5)	110 (54.5)	202 (100.0)		81 (44.0)	103 (56.0)	184 (100.0)		79 (43.6)	102 (56.4)	181 (100.0)	
	Advanced frailty	302 (74.6)	103 (25.4)	405 (100.0)		198 (69.7)	86 (30.3)	284 (100.0)		170 (69.4)	75 (30.6)	245 (100.0)	
	Organ Failure	223 (64.8)	121 (35.2)	344 (100.0)		156 (58.2)	112 (41.8)	268 (100.0)		145 (57.3)	108 (42.7)	253 (100.0)	
	Total	651 (61.5)	408 (38.5)	1059 (100.0)		464 (55.4)	373 (44.6)	837 (100.0)		423 (54.2)	357 (45.8)	780 (100.0)	

Table 14. Mortality rates per advanced chronic condition at 3, 6, 12 and 24 months within main groups (cohort, SQ+ and NECPAL+).
L indicates living; D: deceased.

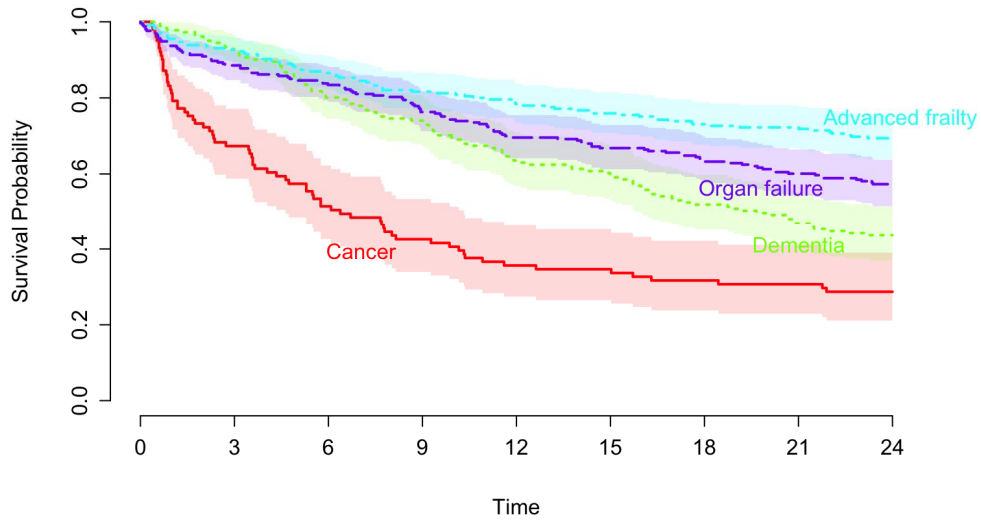

Figure 16. Comparison of survival per advanced chronic condition within NECPAL+ individuals (Log rank test: chi-square 82.350, p-value=0.000).

Finally, significantly different mortality rates were observed among NECPAL+ individuals per setting of care (Table 15 and Figure 17), with higher mortality rates within individuals recruited in intermediate care centre and acute bed hospital, followed by those recruited in nursing homes and primary care centres, respectively. At 12 months, mortality rates were 67.3% in intermediate care centres, 54.0% in the acute bed hospital, 33.1% in nursing homes, and 28.0% in primary care services (chi-square=44.64, p<0.0001). At 24 months, higher mortality rates were 70.9% in intermediate care centres, 62.0% in the acute bed hospital, 57.8% in nursing homes, and 38.0% in primary care services (chi-square=40.94, p<0.0001). The most common place of death was the intermediate care centre (37.3%), followed by nursing homes (24.1%), home (16.4%), and acute care hospital (16.1%). These significant differences were equally observed among individuals of SQ+ and cohort groups and also at 3 and 6 months within the three main groups.

	n and %	COHORT				SQ+				NECPAL+			
		L	D	Total	p value	L	D	Total	p value	L	D	Total	p value
3m	Primary care centres	686 (94.4)	41 (5.6)	727 (100.0)	p<.0001	516 (93.1)	38 (6.9)	554 (100.0)	p<.0001	483 (92.7)	38 (7.3)	521 (100.0)	p<.0001
	Intermediate care centre	50 (67.6)	24 (32.4)	74 (100.0)		31 (56.4)	24 (43.6)	55 (100.0)		31 (56.4)	24 (43.6)	55 (100.0)	
	Acute bed hospital	38 (70.4)	16 (29.6)	54 (100.0)		35 (68.6)	16 (31.4)	51 (100.0)		34 (68.0)	16 (32.0)	50 (100.0)	
	Nursing homes	186 (91.2)	18 (8.8)	204 (100.0)		159 (89.8)	18 (10.2)	177 (100.0)		138 (89.6)	16 (10.4)	154 (100.0)	
	Total	960 (90.7)	99 (9.3)	1059 (100.0)		741 (88.5)	96 (11.5)	837 (100.0)		686 (87.9)	94 (12.1)	780 (100.0)	
6m	Primary care centres	645 (88.7)	82 (11.3)	727 (100.0)	p<.0001	477 (86.1)	77 (13.9)	554 (100.0)	p<.0001	445 (85.4)	76 (14.6)	521 (100.0)	p<.0001
	Intermediate care centre	45 (60.8)	29 (39.2)	74 (100.0)		26 (47.3)	29 (52.7)	55 (100.0)		26 (47.3)	29 (52.7)	55 (100.0)	
	Acute bed hospital	33 (61.1)	21 (38.9)	54 (100.0)		30 (58.8)	21 (41.2)	51 (100.0)		29 (58.0)	21 (42.0)	50 (100.0)	
	Nursing homes	167 (81.9)	37 (18.1)	204 (100.0)		140 (79.1)	37 (20.9)	177 (100.0)		120 (77.9)	34 (22.1)	154 (100.0)	
	Total	890 (84.0)	169 (16.0)	1059 (100.0)		673 (80.4)	164 (19.6)	837 (100.0)		620 (79.5)	160 (20.5)	780 (100.0)	
12m	Primary care centres	565 (77.7)	162 (22.3)	727 (100.0)	p<.0001	405 (73.1)	149 (26.9)	554 (100.0)	p<.0001	375 (72.0)	146 (28.0)	521 (100.0)	p<.0001
	Intermediate care centre	34 (45.9)	40 (54.1)	74 (100.0)		18 (32.7)	37 (67.3)	55 (100.0)		18 (32.7)	37 (67.3)	55 (100.0)	
	Acute bed hospital	27 (50.0)	27 (50.0)	54 (100.0)		24 (47.1)	27 (52.9)	51 (100.0)		23 (46.0)	27 (54.0)	50 (100.0)	
	Nursing homes	147 (72.1)	57 (27.9)	204 (100.0)		122 (68.9)	55 (31.1)	177 (100.0)		103 (66.9)	51 (33.1)	154 (100.0)	
	Total	773 (73.0)	286 (27.0)	1059 (100.0)		569 (68.0)	268 (32.0)	837 (100.0)		519 (66.5)	261 (33.5)	780 (100.0)	
24m	Primary care centres	500 (68.8)	227 (31.2)	727 (100.0)	p<.0001	351 (63.4)	203 (36.6)	554 (100.0)	p<.0001	323 (62.0)	198 (38.0)	521 (100.0)	p<.0001
	Intermediate care centre	29 (39.2)	45 (60.8)	74 (100.0)		16 (29.1)	39 (70.9)	55 (100.0)		16 (29.1)	39 (70.9)	55 (100.0)	
	Acute bed hospital	23 (42.6)	31 (57.4)	54 (100.0)		20 (39.2)	31 (60.8)	51 (100.0)		19 (38.0)	31 (62.0)	50 (100.0)	
	Nursing homes	99 (48.5)	105 (51.5)	204 (100.0)		77 (43.5)	100 (56.5)	177 (100.0)		65 (42.2)	89 (57.8)	154 (100.0)	
	Total	651 (61.5)	408 (38.5)	1059 (100.0)		464 (55.4)	373 (44.6)	837 (100.0)		423 (54.2)	357 (45.8)	780 (100.0)	

Table 15. Mortality rates per setting of care at 3, 6, 12 and 24 months within main groups (cohort, SQ+ and NECPAL+).
L indicates living; D: deceased.

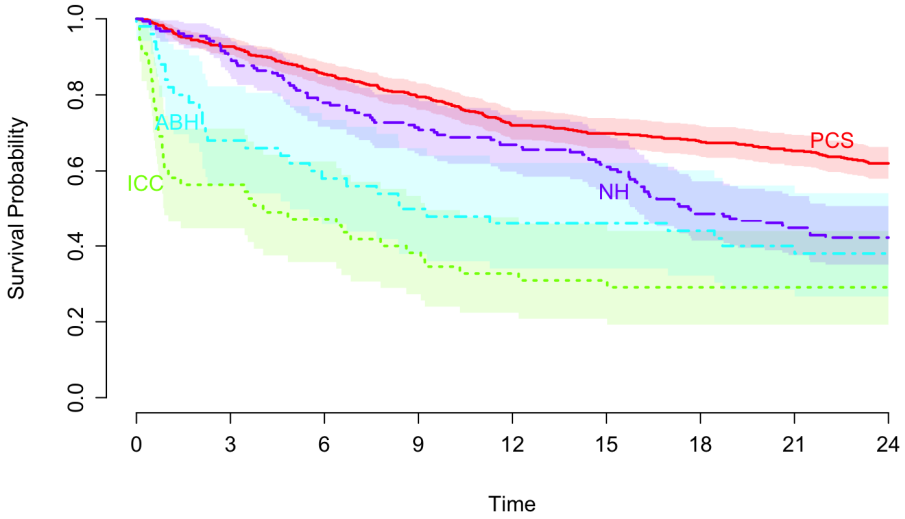

Figure 17. Comparison of survival per setting of care (1=primary care services, 2=intermediate care centre, 3=acute hospital, 4=nursing homes) within NECPAL+ individuals (Log rank test: chi-square 70.570, p-value=0.000).

Validity of the NECPAL CCOMS-ICO© tool as screening tool for early palliative care from a population-based perspective

A total of 1059 individuals were available for survival analysis. Of these, 780 were identified as NECPAL+ and 279 as NECPAL-. Regarding the SQ, 837 were identified as SQ+ and 222 as SQ- (Figure 18).

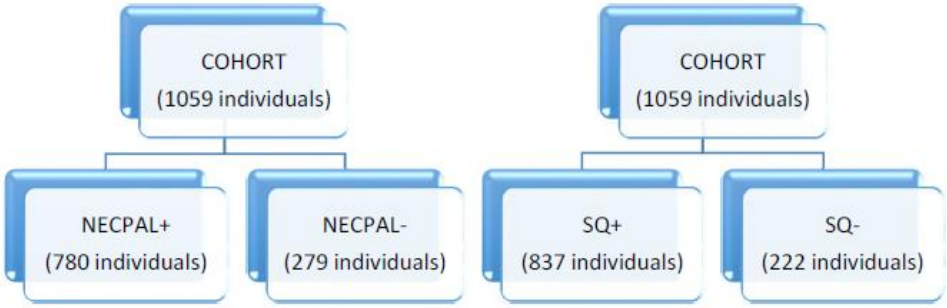

Figure 18. Individuals available for survival analysis classified according to NECPAL and SQ identification.

At 12 months, the mortality rates for NECPAL+ and NECPAL- individuals differed significantly: 33.5% versus 9.0% (chi-square=62.58, p<0.00001). Individuals who were identified as NECPAL+ had 3.73 times the risk of death compared to patients who were identified as NECPAL- (CI: 2.54-5.50). At 24 months, higher mortality rates, of 45.8% versus 18.3%, respectively (chi-square=65.57, p<0.00001) and a lower risk of death, of 2.50, although more accurate (CI: 1.93-3.25), were observed (Table 16 and Figure 19). This tendency, increasing mortality rates and decreasing risk ratio, improving its accuracy, is consistently observed at consecutive time points analysed (3, 6, 12 and 24 months).

NECPAL tool		L	D	Total	p value	RR (95% CI)
3m n and %	NECPAL+	686 (87.9)	94 (12.1)	780 (100.0)	p<0.00001	6.72 (2.76-16.36)
	NECPAL-	274 (98.2)	5 (1.8)	279 (100.0)		
	Total	960 (90.7)	99 (9.3)	1059 (100.0)		
6m n and %	NECPAL+	620 (79.5)	160 (20.5)	780 (100.0)	p<0.00001	6.36 (3.30-12.27)
	NECPAL-	270 (96.8)	9 (3.2)	279 (100.0)		
	Total	890 (84.0)	169 (16.0)	1059 (100.0)		
12m n and %	NECPAL+	519 (66.5)	261 (33.5)	780 (100.0)	p<0.00001	3.73 (2.54-5.50)
	NECPAL-	254 (91.0)	25 (9.0)	279 (100.0)		
	Total	773 (73.0)	286 (27.0)	1059 (100.0)		
24m n and %	NECPAL+	423 (54.2)	357 (45.8)	780 (100.0)	p<0.00001	2.50 (1.93-3.25)
	NECPAL-	228 (81.7)	51 (18.3)	279 (100.0)		
	Total	651 (61.5)	408 (38.5)	1059 (100.0)		
SQ tool		**L**	**D**	**Total**	**p value**	**RR (95% CI)**
3m n and %	SQ+	741(88.5)	96 (11.5)	837 (100.0)	p<0.00001	8.49 (2.72-26.53)
	SQ -	219 (98.6)	3 (1.4)	222 (100.0)		
	Total	960 (90.7)	99 (9.3)	1059 (100.0)		
6m n and %	SQ +	673 (80.4)	164 (19.6)	837 (100.0)	p<0.00001	8.70 (3.62-20.92)
	SQ -	217 (97.7)	5 (2.3)	222 (100.0)		
	Total	890 (84.0)	169 (16.0)	1059 (100.0)		
12m n and %	SQ +	569 (68.0)	268 (32.0)	837 (100.0)	p<0.00001	3.95 (2.51-6.22)
	SQ -	204 (91.9)	18 (8.1)	222 (100.0)		
	Total	773 (73.0)	286 (27.0)	1059 (100.0)		
24m n and %	SQ +	464 (55.4)	373 (44.6)	837 (100.0)	p<0.00001	2.83 (2.07-3.87)
	SQ -	187 (84.2)	35 (15.8)	222 (100.0)		
	Total	651 (61.5)	408 (38.5)	1059 (100.0)		

Table 16. Mortality rates per NECPAL and SQ identification at 3, 6, 12 and 24 months.
L indicates living; D: deceased; RR Risk Ratio (or Relative Risk).

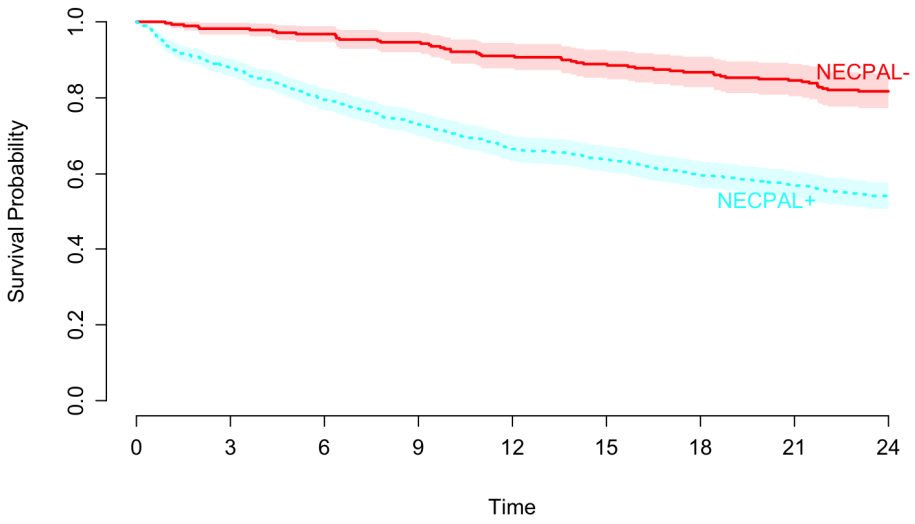

Figure 19. Survival at 24 months: a comparison between NECPAL+ and NECPAL- individuals (Log rank test: chi-square 64.717, p-value=0.000).

Compared to NECPAL identification, the mortality rates observed for SQ+ and SQ- individuals are slightly lower and the risk of death is slightly higher, although less accurate, in SQ+ compared to NECPAL+ individuals, a constant tendency observed at any analysed time point.

At 12 months, the NECPAL CCOMS-ICO© tool presents very high sensitivity (91.3, CI: 87.2-94.2) and very high negative predictive value (NPV) (91.0, CI: 86.9-94.0), with low specificity (32.9, CI: 29.6-36.3), explained by high number of false positives, and low positive predictive value (PPV) (33.5, CI: 30.2-36.9), explained by low number of true positives (low mortality rate) and high number of false positives (Table 17).

At 24 months, it improves specificity (35.0, CI: 31.3-38.7) and PPV (45.8, CI: 42.3-49.3), although they remain low, decreasing sensitivity (87.5, CI: 84.3-90.7) and NPV (81.7, CI: 77.2-86.2).

A tendency to improve specificity and PPV, maintaining high sensitivity and NPV, is consistently observed at consecutive time points analysed (3, 6, 12 and 24 months).

Compared to NECPAL CCOMS-ICO© tool, SQ presents slightly better sensitivity and NPV and slightly worse specificity and PPV at any analysed time point.

Status, n	3m			6m			12m			24m		
NECPAL tool	L	D	Total	L	D	Total	L	D	Total	L	D	Total
NECPAL+	686	94	780	620	160	780	519	261	780	423	357	780
NECPAL-	274	5	279	270	9	279	254	25	279	228	51	279
Total	960	99	1059	890	169	1059	773	286	1059	651	408	1059
Sensitivity, % and 95% CI	94.9 (88.1- 98.1)			94.7 (89.8- 97.3)			91.3 (87.2- 94.2)			87.5 (84.3-90.7)		
Specificity, % and 95% CI	28.5 (25.7- 31.5)			30.3 (27.4- 33.5)			32.9 (29.6- 36.3)			35.0 (31.3-38.7)		
Positive Predictive Value, % and 95% CI	12.1 (9.9- 14.6)			20.5 (17.8- 23.6)			33.5 (30.2- 36.9)			45.8 (42.3-49.3)		
Negative Predictive Value, % and 95% CI	98.2 (95.6- 99.3)			96.8 (93.8- 98.4)			91.0 (86.9- 94.0)			81.7 (77.2-86.2)		
Status, n	3m			6m			12m			24m		
SQ tool	L	D	Total	L	D	Total	L	D	Total	L	D	Total
SQ+	741	96	837	673	164	837	569	268	837	464	373	837
SQ-	219	3	222	217	5	222	204	18	222	187	35	222
Total	960	99	1059	890	169	1059	773	286	1059	651	408	1059
Sensitivity, % and 95% CI	97.0 (90.8-99.2)			97.0 (92.9-98.9)			93.7 (90.1-96.1)			91.4 (88.7-94.1)		
Specificity, % and 95% CI	22.8 (20.2-25.6)			24.4 (21.6-27.4)			26.4 (23.3-30.0)			28.7 (25.2-32.2)		
Positive Predictive Value, % and 95% CI	11.5 (9.4-13.9)			19.6 (17.0-22.5)			32.0 (29.0-35.3)			44.6 (41.2-48.0)		
Negative Predictive Value, % and 95% CI	98.6 (95.8-99.7)			97.7 (94.5-99.2)			91.9 (87.3-95.0)			84.2 (79.4-89.0)		

Table 17. Sensitivity, specificity, and predictive values of NECPAL CCOMS-ICO© tool and SQ at 3, 6, 12 and 24 months (1059 evaluable cases).
L indicates living; D: deceased.

Exploring the validity of the NECPAL CCOMS-ICO© tool as screening tool for early palliative care per advanced chronic condition

Cancer

A small sample of 108 individuals with cancer were available for survival analysis. Of these, 101 were identified as NECPAL+ and 7 as NECPAL-, with the same classification among SQ individuals (101 SQ+ and 7 SQ-).

At 12 months, the mortality rates for NECPAL+ and NECPAL- individuals with cancer were non-significantly different: 64.4% versus 28.6% (Fisher, p=0.10). Individuals who were identified as NECPAL+ had 2.25 times the risk of death compared to patients who were identified as NECPAL-. Nevertheless, confidence interval encompasses 1 (CI: 0.69-7.33), which suggests no difference in risk of death, that is to say that mortality in each group is the same (Table 18).

At 24 months, higher mortality rates and significantly different, of 71.3% versus 28.6% (Fisher, p=0.031) were observed. NECPAL+ individuals with cancer had 2.50 times the risk of death compared to patients who were identified as NECPAL-. Nevertheless, again confidence interval encompasses 1 (CI: 0.77-8.10), which suggests no difference o little difference in risk of death between groups.

Consistently with these results, survival curves for NECPAL+ and NECPAL- individuals (Figure 20) were almost non-significantly different, a comparison result which is probably influenced by the small simple size among NECPAL- individuals.

The same results were observed per SQ identification.

NECPAL tool		L	D	Total	p value	RR (95% CI)
3m n and %	NECPAL+	68 (67.3)	33 (32.7)	101 (100.0)	p=0.098	NA
	NECPAL-	7 (100.0)	0 (0.0)	7 (100.0)		
	Total	75 (69.4)	33 (30.6)	108 (100.0)		
6m n and %	NECPAL+	52 (51.5)	49 (48.5)	101 (100.0)	p=0.120	3.40 (0.55-21.08)
	NECPAL-	6 (85.7)	1 (14.3)	7 (100.0)		
	Total	58 (53.7)	50 (46.3)	108 (100.0)		
12m n and %	NECPAL+	36 (35.6)	65 (64.4)	101 (100.0)	p=0.102	2.25 (0.69-7.33)
	NECPAL-	5 (71.4)	2 (28.6)	7 (100.0)		
	Total	41 (38.0)	67 (62.0)	108 (100.0)		
24m n and %	NECPAL+	29 (28.7)	72 (71.3)	101 (100.0)	p=0.031	2.50 (0.77-8.10)
	NECPAL-	5 (71.4)	2 (28.6)	7 (100.0)		
	Total	34 (31.5)	74 (68.5)	108 (100.0)		
SQ tool		L	D	Total	p value	RR (95% CI)
3m n and %	SQ+	68 (67.3)	33 (32.7)	101 (100.0)	p=0.098	NA
	SQ -	7 (100.0)	0 (0.0)	7 (100.0)		
	Total	75 (69.4)	33 (30.6)	108 (100.0)		
6m n and %	SQ +	52 (51.5)	49 (48.5)	101 (100.0)	p=0.120	3.40 (0.55-21.08)
	SQ -	6 (85.7)	1 (14.3)	7 (100.0)		
	Total	58 (53.7)	50 (46.3)	108 (100.0)		
12m n and %	SQ +	36 (35.6)	65 (64.4)	101 (100.0)	p=0.102	2.25 (0.69-7.33)
	SQ -	5 (71.4)	2 (28.6)	7 (100.0)		
	Total	41 (38.0)	67 (62.0)	108 (100.0)		
24m n and %	SQ +	29 (28.7)	72 (71.3)	101 (100.0)	p=0.031	2.50 (0.77-8.10)
	SQ -	5 (71.4)	2 (28.6)	7 (100.0)		
	Total	34 (31.5)	74 (68.5)	108 (100.0)		

Table 18. Mortality rates per NECPAL and SQ identification in cancer at 3, 6, 12 and 24 months. L indicates living; D: deceased; RR Risk Ratio (or Relative Risk).

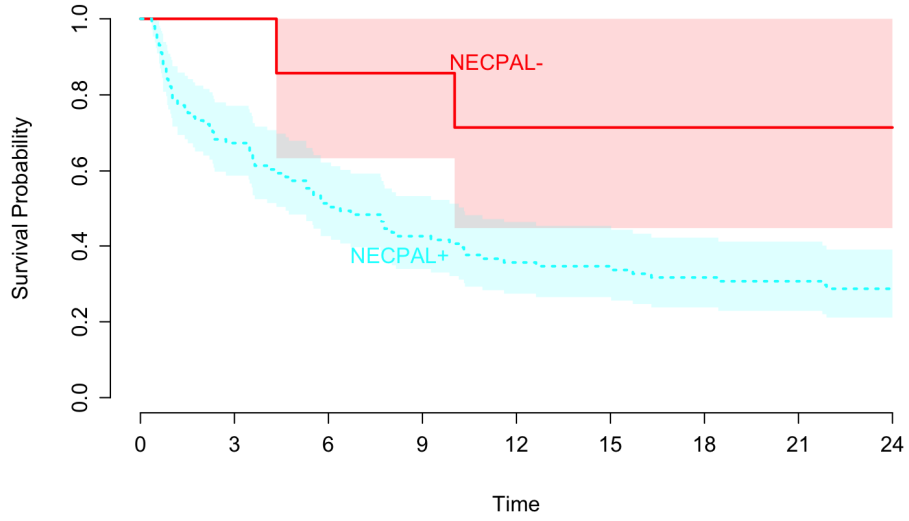

Figure 20. Survival at 24 months: a comparison between NECPAL+ and NECPAL- individuals with cancer (Log rank test: chi-square 4.0, p-value=0.0446).

At 12 months, the NECPAL CCOMS-ICO© tool presents very high sensitivity (97.0, CI: 88.7-99.5) and acceptable although inaccurate NPV (71.4, CI: 30.3-94.9), explained by number of false negatives; with acceptable PPV (64.4, CI: 54.1-73.5), explained by high number of true positives (moderate mortality rate), and very low specificity (12.2, CI: 4.6-27.0), explained by high number of false positives (Table 19).

This predictive validity improves at 24 months (sensitivity: 97.3, CI: 89.7-99.5; NPV: 71.4, CI: 30.3-94.9; specificity: 14.7, CI: 5.5-31.8 and PPV: 71.3, CI: 61.3-79.6), explained by increase of true positives (increase of mortality rate) although specificity remains very low because of high number of false positives.

A tendency to improve slightly specificity and clearly PPV, maintaining high sensitivity and acceptable NPV, is consistently observed at consecutive time points analysed (3, 6, 12 and 24 months).

Compared to NECPAL CCOMS-ICO© tool, SQ presents the same results, as positive and negative identification were exactly the same for both tools (101 vs 7).

Status, n	3m			6m			12m			24m		
NECPAL tool	L	D	Total	L	D	Total	L	D	Total	L	D	Total
NECPAL+	68	33	101	52	49	101	36	65	101	29	72	101
NECPAL-	7	0	7	6	1	7	5	2	7	5	2	7
Total	75	33	108	58	50	108	41	67	108	34	74	108
Sensitivity, % and 95% CI	100 (87.0-100)			98.0 (88.0-99.9)			97.0 (88.7-99.5)			97.3 (89.7-99.5)		
Specificity, % and 95% CI	9.3 (4.2-18.9)			10.3 (4.3-21.8)			12.2 (4.6-27.0)			14.7 (5.5-31.8)		
Positive Predictive Value, % and 95% CI	32.7 (23.9-42.8)			48.5 (38.5-58.6)			64.4 (54.1-73.5)			71.3 (61.3-79.6)		
Negative Predictive Value, % and 95% CI	100 (56.1-100)			85.7 (42.0-99.2)			71.4 (30.3-94.9)			71.4 (30.3-94.9)		
Status, n	**3m**			**6m**			**12m**			**24m**		
SQ tool	L	D	Total	L	D	Total	L	D	Total	L	D	Total
SQ+	68	33	101	52	49	101	36	65	101	29	72	101
SQ-	7	0	7	6	1	7	5	2	7	5	2	7
Total	75	33	108	58	50	108	41	67	108	34	74	108
Sensitivity, % and 95% CI	100 (87.0-100)			98.0 (88.0-99.9)			97.0 (88.7-99.5)			97.3 (89.7-99.5)		
Specificity, % and 95% CI	9.3 (4.2-18.9)			10.3 (4.3-21.8)			12.2 (4.6-27.0)			14.7 (5.5-31.8)		
Positive Predictive Value, % and 95% CI	32.7 (23.9-42.8)			48.5 (38.5-58.6)			64.4 (54.1-73.5)			71.3 (61.3-79.6)		
Negative Predictive Value, % and 95% CI	100 (56.1-100)			85.7 (42.0-99.2)			71.4 (30.3-94.9)			71.4 (30.3-94.9)		

Table 19. Sensitivity, specificity, and predictive values of NECPAL CCOMS-ICO© tool and SQ in cancer at 3, 6, 12 and 24 months (108 evaluable cases).
L indicates living; D: deceased.

Dementia

A relatively small sample of 202 individuals with dementia were available for survival analysis. Of these, 181 were identified as NECPAL+ and 21 as NECPAL-. Regarding the SQ, 184 were identified as SQ+ and 18 as SQ-.

At 12 months, the mortality rates for NECPAL+ and NECPAL- individuals with dementia were non-significantly different: 36.5% versus 14.3% (chi-square=4.12, p=0.074). Individuals who were identified as NECPAL+ had 2.55 times the risk of death compared to patients who were identified as NECPAL-. Nevertheless, confidence interval encompasses 1 (CI: 0.88-7.41), which suggests no difference in risk of death, that is to say that mortality in each group is the same (Table 20).

At 24 months, higher mortality rates although non-significantly different, of 56.4% versus 38.1% (chi-square=2.53, p=0.112) were observed. The risk of death among individuals identified as NECPAL+ was 1.48 times as high as the risk of death among individuals identified as NECPAL-. Nevertheless, again confidence interval encompasses 1 (CI: 0.84-2.59), which suggests no difference in risk of death between groups.

Consistently with these results, survival curves for NECPAL+ and NECPAL- individuals (Figure 21) were non-significantly different.

Compared to NECPAL identification, the mortality rates observed for SQ+ and SQ- individuals are slightly lower among SQ+ and slightly higher among SQ-; and the relative risks of death, and their accuracy, are quite the same at any analysed time point.

NECPAL tool		L	D	Total	p value	RR (95% CI)
3m n and %	NECPAL+	167 (92.3)	14 (7.7)	181 (100.0)	p=1.000	1.62 (0.22-11.74)
	NECPAL-	20 (95.2)	1 (4.8)	21 (100.0)		
	Total	187 (92.6)	15 (7.4)	202 (100.0)		
6m n and %	NECPAL+	145 (80.1)	36 (19.9)	181 (100.0)	p=0.134	4.18 (0.60-28.92)
	NECPAL-	20 (95.2)	1 (4.8)	21 (100.0)		
	Total	165 (81.7)	37 (18.3)	202 (100.0)		
12m n and %	NECPAL+	115 (63.5)	66 (36.5)	181 (100.0)	p=0.074	2.55 (0.88-7.41)
	NECPAL-	18 (85.7)	3 (14.3)	21 (100.0)		
	Total	133 (65.8)	69 (34.2)	202 (100.0)		
24m n and %	NECPAL+	79 (43.6)	102 (56.4)	181 (100.0)	p=0.112	1.48 (0.84-2.59)
	NECPAL-	13 (61.9)	8 (38.1)	21 (100.0)		
	Total	92 (45.5)	110 (54.5)	202 (100.0)		
SQ tool		**L**	**D**	**Total**	**p value**	**RR (95% CI)**
3m n and %	SQ+	170 (92.4)	14 (7.6)	184 (100.0)	p=1.000	1.37 (0.19-9.82)
	SQ -	17 (94.4)	1 (5.6)	18 (100.0)		
	Total	187 (92.6)	15 (7.4)	202 (100.0)		
6m n and %	SQ +	148 (80.4)	36 (19.6)	184 (100.0)	p=0.206	3.52 (0.51-24.19)
	SQ -	17 (94.4)	1 (5.6)	18 (100.0)		
	Total	165 (81.7)	37 (18.3)	202 (100.0)		
12m n and %	SQ +	118 (64.1)	66 (35.9)	184 (100.0)	p=0.101	2.15 (0.75-6.16)
	SQ -	15 (83.3)	3 (16.7)	18 (100.0)		
	Total	133 (65.8)	69 (34.2)	202 (100.0)		
24m n and %	SQ +	81 (44.0)	103 (56.0)	184 (100.0)	p=0.165	1.44 (0.80-2.60)
	SQ -	11 (61.1)	7 (38.9)	18 (100.0)		
	Total	92 (45.5)	110 (54.5)	202 (100.0)		

Table 20. Mortality rates per NECPAL and SQ identification in dementia at 3, 6, 12 and 24 months. L indicates living; D: deceased; RR Risk Ratio (or Relative Risk).

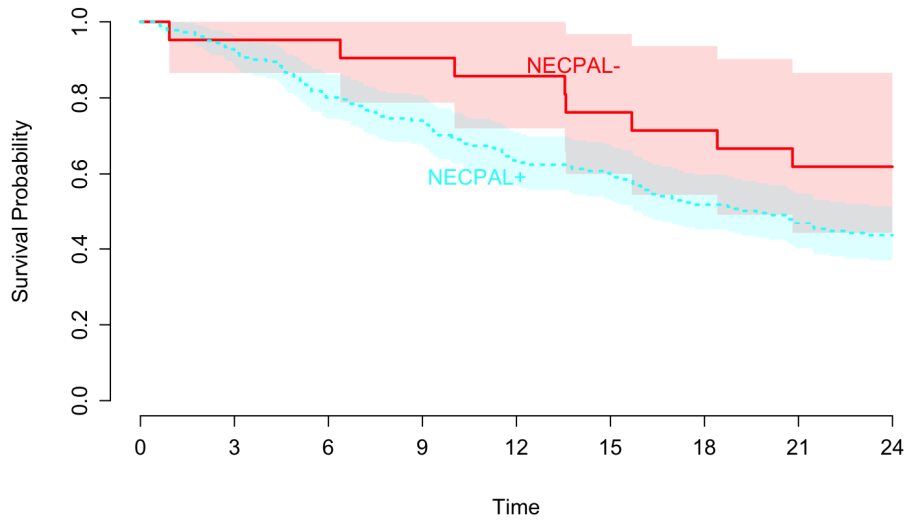

Figure 21. Survival at 24 months: a comparison between NECPAL+ and NECPAL- individuals with dementia (Log rank test: chi-square 2.6, p-value=0.11).

At 12 months, the NECPAL CCOMS-ICO© tool presents very high sensitivity (95.7, CI: 87.0-98.9) and high NPV (85.7, CI: 62.6-96.2), with very low specificity (13.5, CI: 8.4-20.8), explained by high number of false positives, and low PPV (36.5, CI: 29.5-44.0), explained by low number of true positives (low mortality rate) and high number of false positives (Table 21).

This predictive validity changes at 24 months improving PPV (56.4, CI: 48.8-63.6), explained by an increase of true positives (increase of mortality rate), but worsening NPV, included accuracy, (61.9, CI: 38.7-81.0), explained by an increase of false negatives; maintaining very high sensitivity (92.7, CI: 85.7-96.6) and very low specificity (14.1, CI: 8.0-23.3)

A tendency to improve slightly specificity and PPV, maintaining high sensitivity and NPV (except at 24 months), is consistently observed at consecutive time points analysed (3, 6, 12 and 24 months).

Compared to NECPAL CCOMS-ICO© tool, SQ presents slightly worse predictive validity at any analysed time point.

Status, n	3m			6m			12m			24m		
NECPAL tool	L	D	Total	L	D	Total	L	D	Total	L	D	Total
NECPAL+	167	14	181	145	36	181	115	66	181	79	102	181
NECPAL-	20	1	21	20	1	21	18	3	21	13	8	21
Total	187	15	202	165	37	202	133	69	202	92	110	202
Sensitivity, % and 95% CI	93.3 (66.0-99.7)			97.3 (84.2-99.9)			95.7 (87.0-98.9)			92.7 (85.7-96.6)		
Specificity, % and 95% CI	10.7 (6.8-16.3)			12.1 (7.7-18.3)			13.5 (8.4-20.8)			14.1 (8.0-23.3)		
Positive Predictive Value, % and 95% CI	7.7 (4.5-12.9)			19.9 (14.5-26.6)			36.5 (29.5-44.0)			56.4 (48.8-63.6)		
Negative Predictive Value, % and 95% CI	95.2 (74.1-99.8)			95.2 (74.1-99.8)			85.7 (62.6-96.2)			61.9 (38.7-81.0)		
Status, n	**3m**			**6m**			**12m**			**24m**		
SQ tool	L	D	Total	L	D	Total	L	D	Total	L	D	Total
SQ+	170	14	184	148	36	184	118	66	184	81	103	184
SQ-	17	1	18	17	1	18	15	3	18	11	7	18
Total	187	15	202	165	37	202	133	69	202	92	110	202
Sensitivity, % and 95% CI	93.3 (66.0-99.7)			97.3 (84.2-99.9)			95.7 (87.0-98.9)			93.6 (86.9-97.2)		
Specificity, % and 95% CI	9.0 (5.5-14.4)			10.3 (6.3-16.2)			11.3 (6.7-18.2)			12.0 (6.4-20.8)		
Positive Predictive Value, % and 95% CI	7.6 (4.4-12.7)			19.6 (14.2-26.2)			35.9 (29.0-43.3)			56.0 (48.5-63.2)		
Negative Predictive Value, % and 95% CI	94.4 (70.6-99.7)			94.4 (70.6-99.7)			83.3 (57.7-95.6)			61.1 (36.1-81.7)		

Table 21. Sensitivity, specificity, and predictive values of NECPAL CCOMS-ICO© tool and SQ in dementia at 3, 6, 12 and 24 months (202 evaluable cases).
L indicates living; D: deceased.

Advanced frailty

A sample of 405 individuals with advanced frailty were available for survival analysis. Of these, 245 were identified as NECPAL+ and 160 as NECPAL-. Regarding the SQ, 284 were identified as SQ+ and 121 as SQ-.

At 12 months, the mortality rates for NECPAL+ and NECPAL- individuals differed significantly: 21.6% versus 8.1% (chi-square=12.95, p=0.0003). Individuals who were identified as NECPAL+ had 2.66 times the risk of death compared to patients who were identified as NECPAL- (CI: 1.50-4.72) (Table 22).

At 24 months, higher mortality rates, of 30.6% versus 17.5%, respectively (chi-square=8.78, p=0.003) and a lower relative risk of death, of 1.75, although more accurate (CI: 1.19-2.57), were observed. This tendency, increasing mortality rates and decreasing risk ratio, improving its accuracy, is consistently observed at consecutive time points analysed (3, 6, 12 and 24 months).

Consistently with these results, survival curves for NECPAL+ and NECPAL- individuals (Figure 22) were significantly different.

Compared to NECPAL identification, the mortality rates observed for SQ+ and SQ- individuals are slightly lower and the relative risk of death is slightly higher, although clearly less accurate, in SQ+ compared to NECPAL+ individuals, a constant tendency observed at any analysed time point.

NECPAL tool		L	D	Total	p value	RR (95% CI)
3m n and %	NECPAL+	227 (92.7)	18 (7.3)	245 (100.0)	p=0.015	3.92 (1.17-13.09)
	NECPAL-	157 (98.1)	3 (1.9)	160 (100.0)		
	Total	384 (94.8)	21 (5.2)	405 (100.0)		
6m n and %	NECPAL+	212 (86.5)	33 (13.5)	245 (100.0)	p=0.001	3.59 (1.54-8.38)
	NECPAL-	154 (96.3)	6 (3.7)	160 (100.0)		
	Total	366 (90.4)	39 (9.6)	405 (100.0)		
12m n and %	NECPAL+	192 (78.4)	53 (21.6)	245 (100.0)	p=0.0003	2.66 (1.50-4.72)
	NECPAL-	147 (91.9)	13 (8.1)	160 (100.0)		
	Total	339 (83.7)	66 (16.3)	405 (100.0)		
24m n and %	NECPAL+	170 (69.4)	75 (30.6)	245 (100.0)	p=0.003	1.75 (1.19-2.57)
	NECPAL-	132 (82.5)	28 (17.5)	160 (100.0)		
	Total	302 (74.6)	103 (25.4)	405 (100.0)		
SQ tool		L	D	Total	p value	RR (95% CI)
3m n and %	SQ+	264 (93.0)	20 (7.0)	284 (100.0)	p=0.010	8.52 (1.16-62.78)
	SQ -	120 (99.0)	1 (1.0)	121 (100.0)		
	Total	384 (94.8)	21 (5.2)	405 (100.0)		
6m n and %	SQ +	247 (87.0)	37 (13.0)	284 (100.0)	p=0.0004	7.88 (1.93-32.18)
	SQ -	119 (98.4)	2 (1.6)	121 (100.0)		
	Total	366 (90.4)	39 (9.6)	405 (100.0)		
12m n and %	SQ +	226 (79.6)	58 (20.4)	284 (100.0)	p=0.0006	3.09 (1.52-6.27)
	SQ -	113 (93.4)	8 (6.6)	121 (100.0)		
	Total	339 (83.7)	66 (16.3)	405 (100.0)		
24m n and %	SQ +	198 (69.7)	86 (30.3)	284 (100.0)	p=0.0006	2.16 (1.34-3.46)
	SQ -	104 (86.0)	17 (14.0)	121 (100.0)		
	Total	302 (74.6)	103 (25.4)	405 (100.0)		

Table 22. Mortality rates per NECPAL and SQ identification in advanced frailty at 3, 6, 12 and 24 months.

L indicates living; D: deceased; RR Risk Ratio (or Relative Risk).

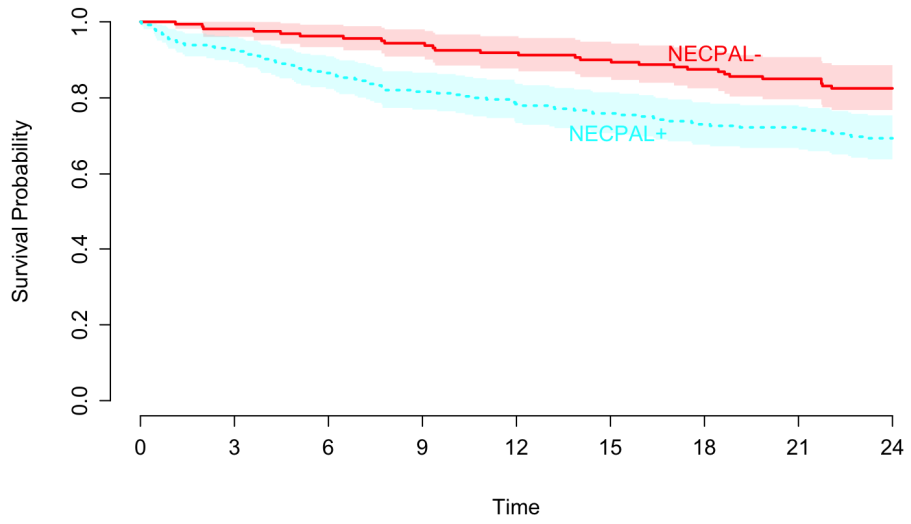

Figure 22. Survival at 24 months: a comparison between NECPAL+ and NECPAL- individuals with advanced frailty (Log rank test: chi-square 9.7, p-value=0.00187).

At 12 months, the NECPAL CCOMS-ICO© tool presents high sensitivity (80.3, CI: 68.3-88.7) and very high NPV (91.9, CI: 86.2-95.4), with low specificity (43.4, CI: 38.0-48.8), explained by high number of false positives, and low PPV (21.6, CI: 16.8-27.4), explained by very low number of true positives (very low mortality rate) and high number of false positives (Table 23).

The predictive validity is worse at 24 months, decreasing sensitivity (72.8, CI: 63.0-80.9) and NPV (82.5, CI: 75.5-87.9, explained by higher number of false negatives, maintaining specificity (43.7, CI: 38.1-49.5) and slightly improving PPV (30.6, CI: 25.0-36.9), explained by higher number of true positives (increase of mortality rate).

A tendency to improve specificity and PPV, maintaining high sensitivity and NPV (except at 24 months), is consistently observed at consecutive time points analysed (3, 6, 12 and 24 months).

Compared to NECPAL CCOMS-ICO© tool, SQ presents slightly better sensitivity and NPV, and slightly worse specificity and PPV at any analysed time point.

Status, n	3m			6m			12m			24m		
NECPAL tool	L	D	Total	L	D	Total	L	D	Total	L	D	Total
NECPAL+	227	18	245	212	33	245	192	53	245	170	75	245
NECPAL-	157	3	160	154	6	160	147	13	160	132	28	160
Total	384	21	405	366	39	405	339	66	405	302	103	405
Sensitivity, % and 95% CI	85.7 (62.6-96.2)			84.6 (68.8-93.6)			80.3 (68.3-88.7)			72.8 (63.0-80.9)		
Specificity, % and 95% CI	40.9 (36.0 (46.0)			42.1 (37.0-47.3)			43.4 (38.0-48.8)			43.7 (38.1-49.5)		
Positive Predictive Value, % and 95% CI	7.3 (4.5-11.6)			13.5 (9.6-18.5)			21.6 (16.8-27.4)			30.6 (25.0-36.9)		
Negative Predictive Value, % and 95% CI	98.1 (94.2-99.5)			96.3 (91.7-98.5)			91.9 (86.2-95.4)			82.5 (75.5-87.9)		
Status, n	3m			6m			12m			24m		
SQ tool	L	D	Total	L	D	Total	L	D	Total	L	D	Total
SQ+	264	20	284	247	37	284	226	58	284	198	86	284
SQ-	120	1	121	119	2	121	113	8	121	104	17	121
Total	384	21	405	366	39	405	339	66	405	302	103	405
Sensitivity, % and 95% CI	95.2 (74.1-99.8)			94.9 (81.4-99.1)			87.9 (77.0-94.3)			83.5 (74.6-89.8)		
Specificity, % and 95% CI	31.3 (26.7-36.2)			32.6 (27.8-37.6)			33.3 (28.4-38.7)			34.4 (29.1-40.1)		
Positive Predictive Value, % and 95% CI	7.0 (4.5-10.8)			13.0 (9.5-17.6)			20.4 (16.0-25.7)			30.3 (25.1-36.0)		
Negative Predictive Value, % and 95% CI	99.2 (94.8-100)			98.3 (93.6-99.7)			93.4 (87.0-96.9)			86.0 (78.2-91.4)		

Table 23. Sensitivity, specificity, and predictive values of NECPAL CCOMS-ICO© tool and SQ in advanced frailty at 3, 6, 12 and 24 months (405 evaluable cases).
L indicates living; D: deceased.

Organ failure

A sample of 344 individuals with organ failure were available for survival analysis. Of these, 253 were identified as NECPAL+ and 91 as NECPAL-. Regarding the SQ, 268 were identified as SQ+ and 76 as SQ-.

At 12 months, the mortality rates for NECPAL+ and NECPAL- individuals differed significantly: 30.4% versus 7.7% (chi-square=18.76, p=0.00001). Individuals who were identified as NECPAL+ had 3.96 times the risk of death compared to patients who were identified as NECPAL- (CI: 1.90-8.26) (Table 24).

At 24 months, higher mortality rates, of 42.7% versus 14.3%, respectively (chi-square=23.68, p=0.00001) and a lower relative risk of death, of 2.99, although more accurate (CI: 1.77-5.04), were observed. This tendency, increasing mortality rates and decreasing risk ratio, improving its accuracy, is not consistently observed at consecutive time points analysed (3, 6, 12 and 24 months) due to an increasing risk ratio, although inaccurate, at 6 months.

Consistently with these results, survival curves for NECPAL+ and NECPAL- individuals (Figure 23) were significantly different.

Compared to NECPAL identification, the mortality rates observed for SQ+ and SQ- individuals are slightly lower. The relative risk of death is slightly lower, and more accurate, at 3 and 6 months; and higher at 12 and 24 months, although less accurate, in SQ+ compared to NECPAL+ individuals.

NECPAL tool		L	D	Total	p value	RR (95% CI)
3m n and %	NECPAL+	224 (88.5)	29 (11.5)	253 (100.0)	p=0.003	10.43 (1.44-75.48)
	NECPAL-	90 (98.9)	1 (1.1)	91 (100.0)		
	Total	314 (91.3)	30 (8.7)	344 (100.0)		
6m n and %	NECPAL+	211 (83.4)	42 (16.6)	253 (100.0)	p=0.0001	15.11 (2.11-108.18)
	NECPAL-	90 (98.9)	1 (1.1)	91 (100.0)		
	Total	301 (87.5)	43 (12.5)	344 (100.0)		
12m n and %	NECPAL+	176 (69.6)	77 (30.4)	253 (100.0)	p=0.00001	3.96 (1.90-8.26)
	NECPAL-	84 (92.3)	7 (7.7)	91 (100.0)		
	Total	260 (75.6)	84 (24.4)	344 (100.0)		
24m n and %	NECPAL+	145 (57.3)	108 (42.7)	253 (100.0)	p<0.00001	2.99 (1.77-5.04)
	NECPAL-	78 (85.7)	13 (14.3)	91 (100.0)		
	Total	223 (64.8)	121 (35.2)	344 (100.0)		
SQ tool		L	D	Total	p value	RR (95% CI)
3m n and %	SQ+	239 (89.2)	29 (10.8)	268 (100.0)	p=0.010	8.22 (1.14-59.39)
	SQ -	75 (98.7)	1 (1.3)	76 (100.0)		
	Total	314 (91.3)	30 (8.7)	344 (100.0)		
6m n and %	SQ +	226 (84.3)	42 (15.7)	268 (100.0)	p=0.0008	11.91 (1.67-85.13)
	SQ -	75 (98.7)	1 (1.3)	76 (100.0)		
	Total	301 (87.5)	43 (12.5)	344 (100.0)		
12m n and %	SQ +	189 (70.5)	79 (29.5)	268 (100.0)	p=0.00004	4.48 (1.88-10.67)
	SQ -	71 (93.4)	5 (6.6)	76 (100.0)		
	Total	260 (75.6)	84 (24.4)	344 (100.0)		
24m n and %	SQ +	156 (58.2)	112 (41.8)	268 (100.0)	p<0.00001	3.53 (1.88-6.62)
	SQ -	67 (88.2)	9 (11.8)	76 (100.0)		
	Total	223 (64.8)	121 (35.2)	344 (100.0)		

Table 24. Mortality rates per NECPAL and SQ identification in organ failure at 3, 6, 12 and 24 months.

L indicates living; D: deceased; RR Risk Ratio (or Relative Risk).

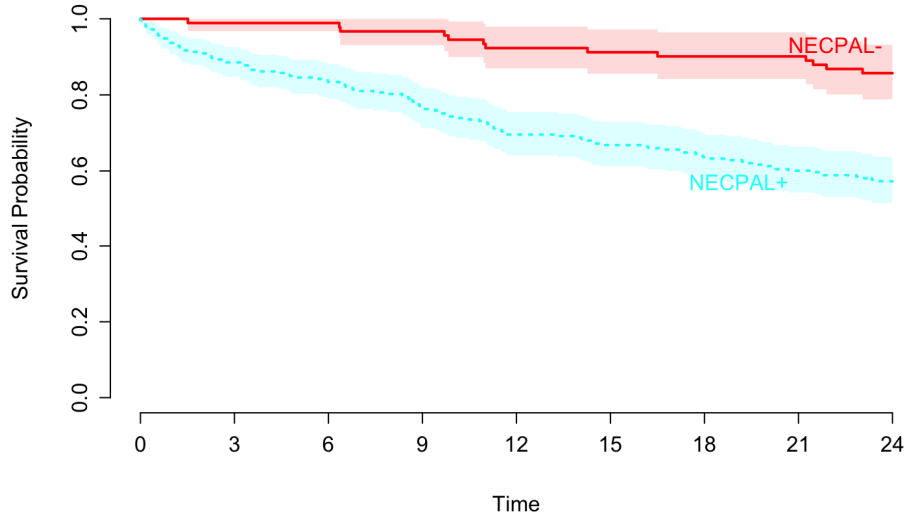

Figure 23. Survival at 24 months: a comparison between NECPAL+ and NECPAL- individuals with organ failure (Log rank test: chi-square 22.9, p-value=1.7e-06).

At 12 months, the NECPAL CCOMS-ICO© tool presents very high sensitivity (91.7, CI: 83.0-96.3) and very high NPV (92.3, CI: 84.3-96.6), with low specificity (32.3, CI: 26.8-38.4), explained by high number of false positives, and low PPV (30.4, CI: 24.9-36.6), explained by very low number of true positives (very low mortality rate) and high number of false positives (Table 25).

At 24 months, it improves specificity (35.0, CI: 28.8-41.7), explained by lower number of false positives, and PPV (45.8, CI: 42.3-49.3), explained by higher number of true positives (increase of mortality rate) and lower number of false positives, although both of them remain low; decreasing sensitivity (87.5, CI: 84.3-90.7) and NPV (81.7, CI: 77.2-86.2), explained by higher number of false negatives.

A tendency to improve specificity and PPV, maintaining high sensitivity and NPV, is consistently observed at consecutive time points analysed (3, 6, 12 and 24 months).

Compared to NECPAL CCOMS-ICO© tool, SQ presents slightly better sensitivity and NPV, and slightly worse specificity and PPV at any analysed time point.

Status, n	3m			6m			12m			24m		
NECPAL tool	L	D	Total	L	D	Total	L	D	Total	L	D	Total
NECPAL+	224	29	253	211	42	253	176	77	253	145	108	253
NECPAL-	90	1	91	90	1	91	84	7	91	78	13	91
Total	314	30	344	301	43	344	260	84	344	223	121	344
Sensitivity, % and 95% CI	96.7 (80.9-99.8)			97.7 (86.2-99.9)			91.7 (83.0-96.3)			89.3 (82.0-93.9)		
Specificity, % and 95% CI	28.7 (23.8-34.1)			29.9 (24.9-35.5)			32.3 (26.8-38.4)			35.0 (28.8-41.7)		
Positive Predictive Value, % and 95% CI	11.5 (7.9-16.2)			16.6 (12.3-21.9)			30.4 (24.9-36.6)			42.7 (36.6-49.0)		
Negative Predictive Value, % and 95% CI	98.9 (93.2-99.9)			98.9 (93.2-99.9)			92.3 (84.3-96.6)			85.7 (76.4-91.9)		
Status, n	3m			6m			12m			24m		
SQ tool	L	D	Total	L	D	Total	L	D	Total	L	D	Total
SQ+	239	29	268	226	42	268	189	79	268	156	112	268
SQ-	75	1	76	75	1	76	71	5	76	67	9	76
Total	314	30	344	301	43	344	260	84	344	223	121	344
Sensitivity, % and 95% CI	96.7 (80.9-99.8)			97.7 (86.2-99.9)			94.0 (86.0-97.8)			92.6 (86.0-96.3)		
Specificity, % and 95% CI	23.9 (19.4-29.1)			24.9 (20.2-30.3)			27.3 (22.1-33.2)			30.0 (24.2-36.6)		
Positive Predictive Value, % and 95% CI	10.8 (7.5-15.3)			15.7 (11.6-20.7)			29.5 (24.2-35.4)			41.8 (35.9-48.0)		
Negative Predictive Value, % and 95% CI	98.7 (91.9-99.9)			98.7 (92.0-99.9)			93.4 (84.7-97.6)			88.2 (78.2-94.1)		

Table 25. Sensitivity, specificity, and predictive values of NECPAL CCOMS-ICO© tool and SQ in organ failure at 3, 6, 12 and 24 months (344 evaluable cases).
L indicates living; D: deceased.

Exploring validity of the NECPAL CCOMS-ICO© tool as screening tool for early palliative care per setting of care

Primary care centres

A sample of 727 individuals recruited at primary care centres were available for survival analysis. Of these, 521 were identified as NECPAL+ and 206 as NECPAL-. Regarding the SQ, 554 were identified as SQ+ and 173 as SQ-.

At 12 months, the mortality rates for NECPAL+ and NECPAL- individuals differed significantly: 28.0% versus 7.8% (chi-square=34.98, $p<0.00001$). Individuals who were identified as NECPAL+ had 3.61 times the risk of death compared to patients who were identified as NECPAL- (CI: 2.21-5.89) (Table 26).

At 24 months, higher mortality rates, of 38.0% versus 14.1%, respectively (chi-square=39.35, $p<0.00001$) and a lower risk of death, of 2.70, although more accurate (CI: 1.89-3.85), were observed. This tendency, increasing mortality rates and decreasing risk ratio, improving its accuracy, is consistently observed at consecutive time points analysed (3, 6, 12 and 24 months).

Consistently with these results, survival curves for NECPAL+ and NECPAL- individuals (Figure 24) were significantly different.

Compared to NECPAL identification, the mortality rates observed for SQ+ and SQ- individuals are slightly lower, as well as the risk ratio, lower in SQ+ compared to NECPAL+ individuals, a constant tendency observed at any analysed time point.

NECPAL tool		L	D	Total	p value	RR (95% CI)
3m n and %	NECPAL+	483 (92.7)	38 (7.3)	521 (100.0)	p=0.002	5.01 (1.56-16.05)
	NECPAL-	203 (98.5)	3 (1.5)	206 (100.0)		
	Total	686 (94.4)	41 (5.6)	727 (100.0)		
6m n and %	NECPAL+	445 (85.4)	76 (14.6)	521 (100.0)	p<0.00001	5.01 (2.22-11.32)
	NECPAL-	200 (97.1)	6 (2.9)	206 (100.0)		
	Total	645 (88.7)	82 (11.3)	727 (100.0)		
12m n and %	NECPAL+	375 (72.0)	146 (28.0)	521 (100.0)	p<0.00001	3.61 (2.21-5.89)
	NECPAL-	190 (92.2)	16 (7.8)	206 (100.0)		
	Total	565 (77.7)	162 (22.3)	727 (100.0)		
24m n and %	NECPAL+	323 (62.0)	198 (38.0)	521 (100.0)	p<0.00001	2.70 (1.89-3.85)
	NECPAL-	177 (85.9)	29 (14.1)	206 (100.0)		
	Total	500 (68.8)	227 (31.2)	727 (100.0)		
SQ tool		L	D	Total	p value	RR (95% CI)
3m n and %	SQ+	516 (93.1)	38 (6.9)	554 (100.0)	p=0.011	3.96 (1.24-12.66)
	SQ -	170 (98.3)	3 (1.7)	173 (100.0)		
	Total	686 (94.4)	41 (5.6)	727 (100.0)		
6m n and %	SQ +	477 (86.1)	77 (13.9)	554 (100.0)	p=0.00006	4.81 (1.98-11.69)
	SQ -	168 (97.1)	5 (2.9)	173 (100.0)		
	Total	645 (88.7)	82 (11.3)	727 (100.0)		
12m n and %	SQ +	405 (73.1)	149 (26.9)	554 (100.0)	p<0.00001	3.58 (2.08-6.15)
	SQ -	160 (92.5)	13 (7.5)	173 (100.0)		
	Total	565 (77.7)	162 (22.3)	727 (100.0)		
24m n and %	SQ +	351 (63.4)	203 (36.6)	554 (100.0)	p<0.00001	2.64 (1.79-3.89)
	SQ -	149 (86.1)	24 (13.9)	173 (100.0)		
	Total	500 (68.8)	227 (31.2)	727 (100.0)		

Table 26. Mortality rates per NECPAL and SQ identification in primary care centres at 3, 6, 12 and 24 months.
L indicates living; D: deceased; RR Risk Ratio (or Relative Risk).

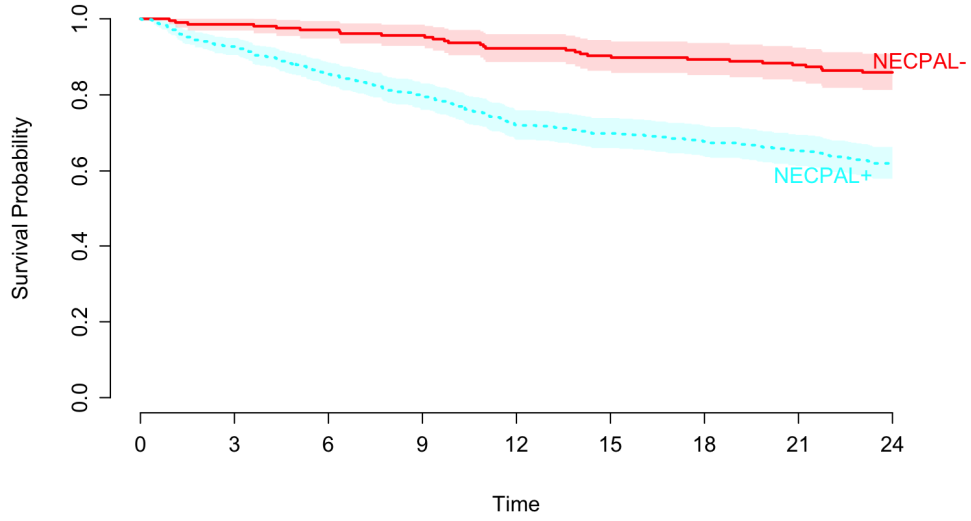

Figure 24. Survival at 24 months: a comparison between NECPAL+ and NECPAL- individuals in primary care (Log rank test: chi-square 38.2, p-value=6.41e-10).

At 12 months, the NECPAL CCOMS-ICO© tool presents very high sensitivity (90.1, CI: 84.2-94.1) and very high NPV (92.2, CI: 87.5-95.4), with low specificity (33.6, CI: 29.8-37.7), explained by high number of false positives, and low PPV (28.0, CI: 24.2-32.1), explained by very low number of true positives (very low mortality rate) and high number of false positives (Table 27).

At 24 months, it improves specificity (35.4, CI: 31.2-39.8), explained by lower number of false positives, and PPV (38.0, CI: 33.8-42.3), explained by higher number of true positives (increase of mortality rate) and lower number of false positives, although both of them remain low; decreasing sensitivity (87.2, CI: 82.0-91.1) and NPV (86.0, CI: 80.2-90.2), explained by higher number of false negatives.

A tendency to improve specificity and PPV, maintaining high sensitivity and NPV, is consistently observed at consecutive time points analysed (3, 6, 12 and 24 months).

Compared to NECPAL CCOMS-ICO© tool, SQ presents slightly better sensitivity and NPV, and slightly worse specificity and PPV at any analysed time point.

Status, n	3m			6m			12m			24m		
NECPAL tool	L	D	Total	L	D	Total	L	D	Total	L	D	Total
NECPAL+	483	38	521	445	76	521	375	146	521	323	198	521
NECPAL-	203	3	206	200	6	206	190	16	206	177	29	206
Total	686	41	727	645	82	727	565	162	727	500	227	727
Sensitivity, % and 95% CI	92.7 (79.0-98.1)			92.7 (84.2-97.0)			90.1 (84.2-94.1)			87.2 (82.0-91.1)		
Specificity, % and 95% CI	29.6 (26.2-33.2)			31.0 (27.5-34.8)			33.6 (29.8-37.7)			35.4 (31.2-39.8)		
Positive Predictive Value, % and 95% CI	7.3 (5.3-10.0)			14.6 (11.7-18.0)			28.0 (24.2-32.1)			38.0 (33.8-42.3)		
Negative Predictive Value, % and 95% CI	98.5 (95.5-99.6)			97.1 (93.5-98.8)			92.2 (87.5-95.4)			86.0 (80.2-90.2)		
Status, n	**3m**			**6m**			**12m**			**24m**		
SQ tool	L	D	Total	L	D	Total	L	D	Total	L	D	Total
SQ+	516	38	554	477	77	554	405	149	554	351	203	554
SQ-	170	3	173	168	5	173	160	13	173	149	24	173
Total	686	41	727	645	82	727	565	162	727	500	227	727
Sensitivity, % and 95% CI	92.7 (79.0-98.1)			93.9 (85.7-97.7)			92.0 (86.4-95.5)			89.4 (84.5-93.0)		
Specificity, % and 95% CI	24.8 (21.6-28.2)			26.0 (22.7-29.6)			28.3 (24.7-32.3)			29.8 (25.9-34.1)		
Positive Predictive Value, % and 95% CI	6.9 (5.0-9.4)			13.9 (11.2-17.1)			26.9 (23.3-30.8)			36.6 (32.6-40.8)		
Negative Predictive Value, % and 95% CI	98.3 (94.6-99.6)			97.1 (93.0-98.9)			92.5 (87.2-95.8)			86.1 (79.9-90.7)		

Table 27. Sensitivity, specificity, and predictive values of NECPAL CCOMS-ICO© tool and SQ in primary care centres at 3, 6, 12 and 24 months (727 evaluable cases).
L indicates living; D: deceased.

Intermediate care centre

A small sample of 74 individuals recruited at intermediate care centre were available for survival analysis. Of these, 55 were identified as NECPAL+ and 19 as NECPAL-, with the same classification among SQ individuals (55 SQ+ and 19 SQ-).

At 12 months, the mortality rates for NECPAL+ and NECPAL- individuals differed significantly: 67.3% versus 15.8% (chi-square=15.07, p=0.0001). Individuals who were identified as NECPAL+ had 4.26 times the risk of death compared to patients who were identified as NECPAL- (CI: 1.48-12.23) (Table 28).

At 24 months, higher mortality rates, of 70.9% versus 31.6%, respectively (chi-square=9.17, p=0.0025) and a lower risk of death, of 2.25, although more accurate (CI: 1.13-4.45), were observed. This tendency, increasing mortality rates and decreasing risk ratio, improving its accuracy, is consistently observed at consecutive time points analysed (12 and 24 months). At 3 and 6 moths, risk ratio was not calculable due to the absence of deaths among NECPAL- individuals.

Consistently with these results, survival curves for NECPAL+ and NECPAL- individuals (Figure 25) were significantly different.

The same results were observed per SQ identification.

NECPAL tool		L	D	Total	p value	RR (95% CI)
3m n and %	NECPAL+	31 (56.4)	24 (43.6)	55 (100.0)	p=0.0005	NA
	NECPAL-	19 (100.0)	0 (0.0)	19 (100.0)		
	Total	50 (67.6)	24 (32.4)	74 (100.0)		
6m n and %	NECPAL+	26 (47.3)	29 (52.7)	55 (100.0)	p=0.00005	NA
	NECPAL-	19 (100.0)	0 (0.0)	19 (100.0)		
	Total	45 (60.8)	29 (39.2)	74 (100.0)		
12m n and %	NECPAL+	18 (32.7)	37 (67.3)	55 (100.0)	p=0.0001	4.26 (1.48-12.23)
	NECPAL-	16 (84.2)	3 (15.8)	19 (100.0)		
	Total	34 (46.0)	40 (54.0)	74 (100.0)		
24m n and %	NECPAL+	16 (29.1)	39 (70.9)	55 (100.0)	p=0.0025	2.25 (1.13-4.45)
	NECPAL-	13 (68.4)	6 (31.6)	19 (100.0)		
	Total	29 (39.2)	45 (60.8)	74 (100.0)		
SQ tool		L	D	Total	p value	RR (95% CI)
3m n and %	SQ+	31 (56.4)	24 (43.6)	55 (100.0)	p=0.0005	NA
	SQ -	19 (100.0)	0 (0.0)	19 (100.0)		
	Total	50 (67.6)	24 (32.4)	74 (100.0)		
6m n and %	SQ +	26 (47.3)	29 (52.7)	55 (100.0)	p=0.00005	NA
	SQ -	19 (100.0)	0 (0.0)	19 (100.0)		
	Total	45 (60.8)	29 (39.2)	74 (100.0)		
12m n and %	SQ +	18 (32.7)	37 (67.3)	55 (100.0)	p=0.0001	4.26 (1.48-12.23)
	SQ -	16 (84.2)	3 (15.8)	19 (100.0)		
	Total	34 (46.0)	40 (54.0)	74 (100.0)		
24m n and %	SQ +	16 (29.1)	39 (70.9)	55 (100.0)	p=0.0025	2.25 (1.13-4.45)
	SQ -	13 (68.4)	6 (31.6)	19 (100.0)		
	Total	29 (39.2)	45 (60.8)	74 (100.0)		

Table 28. Mortality rates per NECPAL and SQ identification in intermediate care centre at 3, 6, 12 and 24 months.
L indicates living; D: deceased; RR Risk Ratio (or Relative Risk).

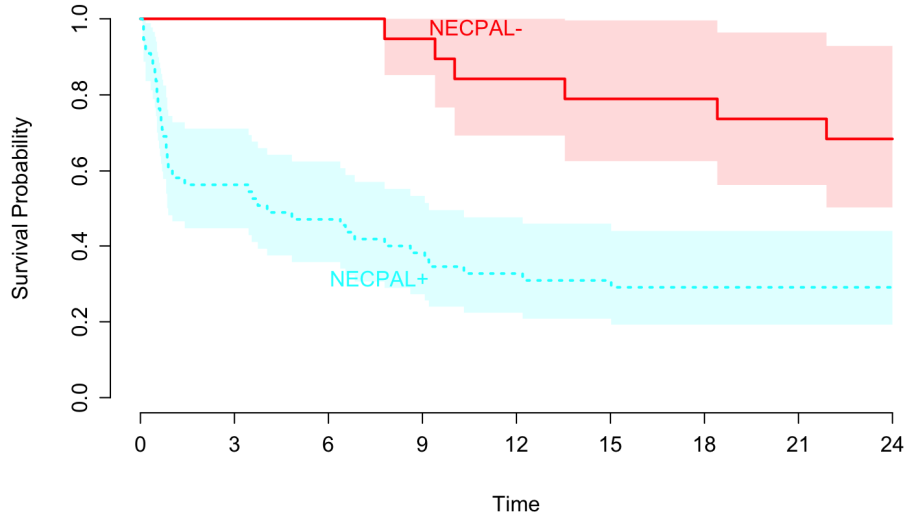

Figure 25. Survival at 24 months: a comparison between NECPAL+ and NECPAL- individuals in intermediate care centre (Log rank test: chi-square 11.3, p-value=0.000787).

At 12 months, the NECPAL CCOMS-ICO© tool presents very high sensitivity (92.5, CI: 78.6-98.0) and high although inaccurate NPV (84.2, CI: 59.5-95.8), with low specificity (47.1, CI: 30.2-64.6), explained by high number of false positives, and acceptable PPV (67.3, CI: 53.2-79.0), explained by high number of true positives (high mortality rate) despite the number of false positives (Table 29).

At 24 months, it improves PPV (70.9, CI: 56.9-82.0), explained by higher number of true positives (slightly increase of mortality rate) and lower number of false positives, decreasing sensitivity (86.7, CI: 72.6-94.5) and NPV (68.4, CI: 43.5-86.5), explained by higher number of false negatives; as well as specificity (44.8, CI: 27.0-64.0), explained by lower number of true negatives.

A tendency to improve specificity and PPV, maintaining high sensitivity and NPV, is consistently observed at consecutive time points analysed (3, 6 and 12

months). Although PPV is higher at 24 months, predictive validity is worse at this time point.

Compared to NECPAL CCOMS-ICO© tool, SQ presents the same results, as positive and negative identification were exactly the same for both tools (55 vs 19).

Status, n	3m			6m			12m			24m		
NECPAL tool	L	D	Total	L	D	Total	L	D	Total	L	D	Total
SQ+	31	24	55	26	29	55	18	37	55	16	39	55
SQ-	19	0	19	19	0	19	16	3	19	13	6	19
Total	50	24	74	45	29	74	34	40	74	29	45	74
Sensitivity, % and 95% CI	100 (82.9-100)			100 (85.4-100)			92.5 (78.6-98.0)			86.7 (72.6-94.5)		
Specificity, % and 95% CI	38.0 (25.0-52.9)			42.2 (28.0-57.8)			47.1 (30.2-64.6)			44.8 (27.0-64.0)		
Positive Predictive Value, % and 95% CI	43.6 (30.6-57.6)			52.7 (38.9-66.1)			67.3 (53.2-79.0)			70.9 (56.9-82.0)		
Negative Predictive Value, % and 95% CI	100 (79.1-100)			100 (79.1-100)			84.2 (59.5-95.8)			68.4 (43.5-86.5)		
Status, n	**3m**			**6m**			**12m**			**24m**		
SQ tool	L	D	Total	L	D	Total	L	D	Total	L	D	Total
NECPAL+	31	24	55	26	29	55	18	37	55	16	39	55
NECPAL-	19	0	19	19	0	19	16	3	19	13	6	19
Total	50	24	74	45	29	74	34	40	74	29	45	74
Sensitivity, % and 95% CI	100 (82.9-100)			100 (85.4-100)			92.5 (78.6-98.0)			86.7 (72.6-94.5)		
Specificity, % and 95% CI	38.0 (25.0-52.9)			42.2 (28.0-57.8)			47.1 (30.2-64.6)			44.8 (27.0-64.0)		
Positive Predictive Value, % and 95% CI	43.6 (30.6-57.6)			52.7 (38.9-66.1)			67.3 (53.2-79.0)			70.9 (56.9-82.0)		
Negative Predictive Value, % and 95% CI	100 (79.1-100)			100 (79.1-100)			84.2 (59.5-95.8)			68.4 (43.5-86.5)		

Table 29. Sensitivity, specificity, and predictive values of NECPAL CCOMS-ICO© tool and SQ in intermediate care centre at 3, 6, 12 and 24 months (74 evaluable cases).
L indicates living; D: deceased.

Acute bed hospital

A small sample of 54 individuals recruited at acute bed hospital were available for survival analysis. Of these, 50 were identified as NECPAL+ and 4 as NECPAL-. Regarding the SQ, 51 were identified as SQ+ and 3 as SQ-.

At 12 months, the mortality rates for NECPAL+ and NECPAL- individuals were non-significantly different: 54.0% versus 0.0% (Fisher, p=0.111). Risk ratio was not calculable at any time point due to the absence of deaths among NECPAL- individuals. (Table 30).

At 24 months, higher mortality rates for NECPAL+ and NECPAL- individuals differed significantly: 62.0% versus 0.0% (Fisher, p=0.028).

Consistently with these results, survival curves for NECPAL+ and NECPAL- individuals (Figure 26) were non-significantly different, a comparison result which is probably influenced by the small simple size and the lack of deaths among NECPAL- individuals.

Compared to NECPAL identification, the mortality rates observed for SQ+ and SQ- individuals are slightly lower among SQ+ and the same among SQ- (absence of deaths among SQ- is also observed), without significant differences at 24 months.

NECPAL tool		L	D	Total	p value	RR (95% CI)
3m n and %	NECPAL+	34 (68.0)	16 (32.0)	50 (100.0)	p=0.306	NA
	NECPAL-	4 (100.0)	0 (0.0)	4 (100.0)		
	Total	38 (70.4)	16 (29.6)	54 (100.0)		
6m n and %	NECPAL+	29 (58.0)	21 (42.0)	50 (100.0)	p=0.148	NA
	NECPAL-	4 (100.0)	0 (0.0)	4 (100.0)		
	Total	33 (61.1)	21 (38.9)	54 (100.0)		
12m n and %	NECPAL+	23 (46.0)	27 (54.0)	50 (100.0)	p=0.111	NA
	NECPAL-	4 (100.0)	0 (0.0)	4 (100.0)		
	Total	27 (50.0)	27 (50.0)	54 (100.0)		
24m n and %	NECPAL+	19 (38.0)	31 (62.0)	50 (100.0)	p=0.028	NA
	NECPAL-	4 (100.0)	0 (0.0)	4 (100.0)		
	Total	23 (42.6)	31 (57.4)	54 (100.0)		
SQ tool		L	D	Total	p value	RR (95% CI)
3m n and %	SQ+	35 (68.6)	16 (31.4)	51 (100.0)	p=0.547	NA
	SQ -	3 (100.0)	0 (0.0)	3 (100.0)		
	Total	38 (70.4)	16 (29.6)	54 (100.0)		
6m n and %	SQ +	30 (58.8)	21 (41.2)	51 (100.0)	p=0.274	NA
	SQ -	3 (100.0)	0 (0.0)	3 (100.0)		
	Total	33 (61.1)	21 (38.9)	54 (100.0)		
12m n and %	SQ +	24 (47.1)	27 (52.9)	51 (100.0)	p=0.236	NA
	SQ -	3 (100.0)	0 (0.0)	3 (100.0)		
	Total	27 (50.0)	27 (50.0)	54 (100.0)		
24m n and %	SQ +	20 (39.2)	31 (60.8)	51 (100.0)	p=0.071	NA
	SQ -	3 (100.0)	0 (0.0)	3 (100.0)		
	Total	23 (42.6)	31 (57.4)	54 (100.0)		

Table 30. Mortality rates per NECPAL and SQ identification in acute bed hospital at 3, 6, 12 and 24 months.
L indicates living; D: deceased; RR Risk Ratio (or Relative Risk).

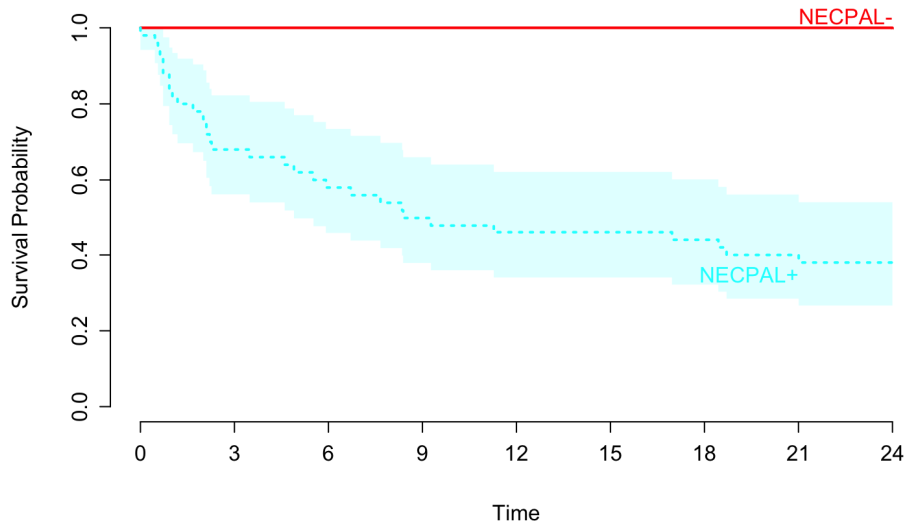

Figure 26. Survival at 24 months: a comparison between NECPAL+ and NECPAL- individuals in acute bed hospital (Log rank test: chi-square 3.8, p-value=0.051).

At 12 months, the NECPAL CCOMS-ICO© tool presents perfect sensitivity (100.0, CI: 84.5-100.0) and perfect although inaccurate NPV (100.0, CI: 39.6-100.0), with very low specificity (14.8, CI: 4.9-34.6), explained by high number of false positives, and acceptable PPV (54.0, CI: 39.5-67.9), explained by considerable number of true positives (moderate mortality rate) although the number of false positives (Table 31).

This predictive validity improves at 24 months increasing PPV (62.0, CI: 47.2-75.0), explained by higher number of true positives (increase of mortality rate) and lower number or false positives, and specificity (17.4, CI: 5.7-39.5), explained by lower number or false positives; maintaining perfect sensitivity (100.0, CI: 86.3-100.0) and perfect although inaccurate NPV (100.0, CI: 39.6-100.0).

A tendency to improve slightly specificity and PPV, maintaining perfect sensitivity and NPV, is consistently observed at consecutive time points analysed (3, 6, 12 and 24 months).

Compared to NECPAL CCOMS-ICO© tool, SQ presents slightly worse predictive validity at any analysed time point.

Status, n	3m			6m			12m			24m		
NECPAL tool	L	D	Total	L	D	Total	L	D	Total	L	D	Total
NECPAL+	34	16	50	29	21	50	23	27	50	19	31	50
NECPAL-	4	0	4	4	0	4	4	0	4	4	0	4
Total	38	16	54	33	21	54	27	27	54	23	31	54
Sensitivity, % and 95% CI	100 (75.9-100)			100 (80.8-100)			100 (84.5-100)			100 (86.3-100)		
Specificity, % and 95% CI	10.5 (3.4-25.7)			12.1 (4.0-29.1)			14.8 (4.9-34.6)			17.4 (5.7-39.5)		
Positive Predictive Value, % and 95% CI	32.0 (19.9-46.8)			42.0 (28.5-56.7)			54.0 (39.5-67.9)			62.0 (47.2-75.0)		
Negative Predictive Value, % and 95% CI	100 (39.6-100)			100 (39.6-100)			100 (39.6-100)			100 (39.6-100)		
Status, n	3m			6m			12m			24m		
SQ tool	L	D	Total	L	D	Total	L	D	Total	L	D	Total
SQ+	35	16	51	30	21	51	24	27	51	20	31	51
SQ-	3	0	3	3	0	3	3	0	3	3	0	3
Total	38	16	54	33	21	54	27	27	54	23	31	54
Sensitivity, % and 95% CI	100 (76.0-100)			100 (80.8-100)			100 (84.5-100)			100 (86.2-100)		
Specificity, % and 95% CI	7.9 (2.1-22.5)			9.1 (2.4-25.5)			11.1 (2.9-30.3)			13.0 (3.4-34.7)		
Positive Predictive Value, % and 95% CI	31.4 (19.5-46.0)			41.2 (27.9-55.8)			52.9 (38.6-66.8)			60.8 (46.1-73.8)		
Negative Predictive Value, % and 95% CI	100 (31.0-100)			100 (31.0-100)			100 (31.0-100)			100 (31.0-100)		

Table 31. Sensitivity, specificity, and predictive values of NECPAL CCOMS-ICO© tool and SQ in acute bed hospital at 3, 6, 12 and 24 months (54 evaluable cases).
L indicates living; D: deceased.

Nursing homes

A relatively small sample of 204 individuals recruited at nursing homes were available for survival analysis. Of these, 154 were identified as NECPAL+ and 50 as NECPAL-. Regarding the SQ, 177 were identified as SQ+ and 27 as SQ-.

At 12 months, the mortality rates for NECPAL+ and NECPAL- individuals differed significantly: 33.1% versus 12.0% (chi-square=8.36, p=0.0038). The risk of death among individuals identified as NECPAL+ was 2.76 times as high as the risk of death among individuals identified as NECPAL- (CI: 1.26-6.04).

At 24 months, higher mortality rates, of 57.8% versus 32.0%, respectively (chi-square=10.05, p=0.0015) and a lower risk of death, of 1.81, although more accurate (CI: 1.18-2.77), were observed (Table 32). This tendency, increasing mortality rates and decreasing risk ratio, improving its accuracy, is consistently observed at consecutive time points analysed (6, 12 and 24 months), except at 3 months.

Consistently with these results, survival curves for NECPAL+ and NECPAL- individuals (Figure 27) were significantly different.

Compared to NECPAL identification, the mortality rates observed for SQ+ and SQ- individuals are slightly lower among SQ+ and clearly lower among SQ-; and risk ratio are slightly higher, although less accurate, in SQ+ compared to NECPAL+ individuals.

NECPAL tool		L	D	Total	p value	RR (95% CI)
3m n and %	NECPAL+	138 (89.6)	16 (10.4)	154 (100.0)	p=0.251	2.60 (0.62-10.91)
	NECPAL-	48 (96.0)	2 (4.0)	50 (100.0)		
	Total	186 (91.2)	18 (8.8)	204 (100.0)		
6m n and %	NECPAL+	120 (77.9)	34 (22.1)	154 (100.0)	p=0.0104	3.68 (1.18-11.47)
	NECPAL-	47 (94.0)	3 (6.0)	50 (100.0)		
	Total	167 (81.9)	37 (18.1)	204 (100.0)		
12m n and %	NECPAL+	103 (66.9)	51 (33.1)	154 (100.0)	p=0.0038	2.76 (1.26-6.04)
	NECPAL-	44 (88.0)	6 (12.0)	50 (100.0)		
	Total	147 (72.1)	57 (27.9)	204 (100.0)		
24m n and %	NECPAL+	65 (42.2)	89 (57.8)	154 (100.0)	p=0.0015	1.81 (1.18-2.77)
	NECPAL-	34 (68.0)	16 (32.0)	50 (100.0)		
	Total	99 (48.5)	105 (51.5)	204 (100.0)		
SQ tool		L	D	Total	p value	RR (95% CI)
3m n and %	SQ+	159 (89.8)	18 (10.2)	177 (100.0)	p=0.138	NA
	SQ -	27 (100.0)	0 (0.0)	27 (100.0)		
	Total	186 (91.2)	18 (8.8)	204 (100.0)		
6m n and %	SQ +	140 (79.1)	37 (20.9)	177 (100.0)	p=0.013	NA
	SQ -	27 (100.0)	0 (0.0)	27 (100.0)		
	Total	167 (81.9)	37 (18.1)	204 (100.0)		
12m n and %	SQ +	122 (69.0)	55 (31.0)	177 (100.0)	p=0.0107	4.19 (1.09-16.21)
	SQ -	25 (92.6)	2 (7.4)	27 (100.0)		
	Total	147 (72.1)	57 (27.9)	204 (100.0)		
24m n and %	SQ +	77 (43.5)	100 (56.5)	177 (100.0)	p=0.0002	3.05 (1.37-6.80)
	SQ -	22 (81.5)	5 (18.5)	27 (100.0)		
	Total	99 (48.5)	105 (51.5)	204 (100.0)		

Table 32. Mortality rates per NECPAL and SQ identification in nursing homes at 3, 6, 12 and 24 months.

L indicates living; D: deceased; RR Risk Ratio (or Relative Risk).

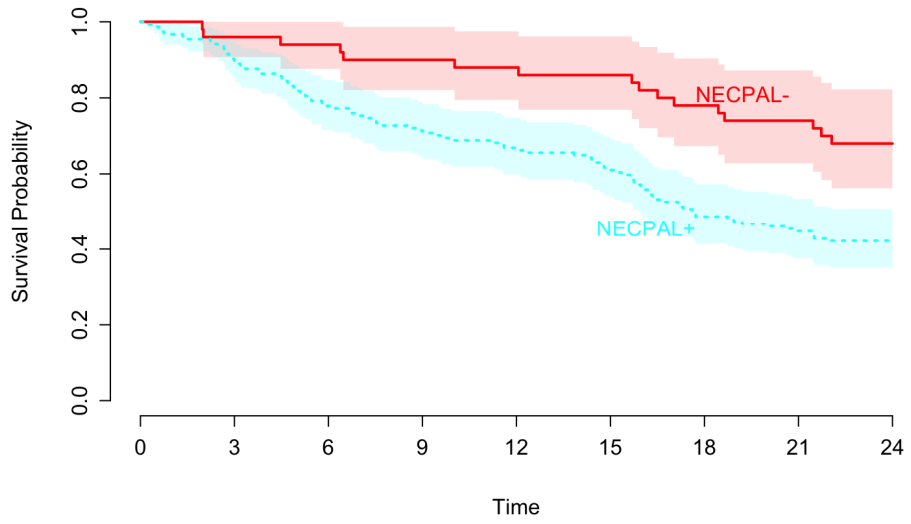

Figure 27. Survival at 24 months: a comparison between NECPAL+ and NECPAL- individuals in nursing homes (Log rank test: chi-square 10.3, p-value=0.00132).

At 12 months, the NECPAL CCOMS-ICO© tool presents high sensitivity (89.5, CI: 77.8-95.6) and high NPV (88.0, CI: 75.0-95.0), with low specificity (29.9, CI: 22.8-38.1), explained by high number of false positives, and low PPV (33.1, CI: 25.9-41.2), explained by low number of true positives (low mortality rate) and high number of false positives (Table 33).

At 24 months, it improves specificity (34.3, CI: 25.3-44.6), explained by lower number of false positives, and clearly improves PPV (57.8, CI: 49.6-65.6), explained by higher number of true positives (increase of mortality rate) and lower number of false positives; maintaining sensitivity (84.8, CI: 76.1-90.8) and clearly worsening NPV (68.0, CI: 53.2-80.1), explained by higher number of false negatives.

A tendency to improve specificity and PPV, maintaining high sensitivity and NPV, is consistently observed at consecutive time points analysed (3, 6 and 12 months), excluding time point at 24 months due to worsening of NPV.

Compared to NECPAL CCOMS-ICO© tool, SQ presents better sensitivity and NPV, included at 24 months, and worse specificity and PPV at any analysed time point.

Status, n	3m			6m			12m			24m		
NECPAL tool	L	D	Total	L	D	Total	L	D	Total	L	D	Total
NECPAL+	138	16	154	120	34	154	103	51	154	65	89	154
NECPAL-	48	2	50	47	3	50	44	6	50	34	16	50
Total	186	18	204	167	37	204	147	57	204	99	105	204
Sensitivity, % and 95% CI	88.9 (63.9-98.1)			91.9 (77.0-97.9)			89.5 (77.8-95.6)			84.8 (76.1-90.8)		
Specificity, % and 95% CI	25.8 (19.8-32.8)			28.1 (21.6-35.7)			29.9 (22.8-38.1)			34.3 (25.3-44.6)		
Positive Predictive Value, % and 95% CI	10.4 (6.2-16.6)			22.1 (16.0-29.6)			33.1 (25.9-41.2)			57.8 (49.6-65.6)		
Negative Predictive Value, % and 95% CI	96.0 (85.1-99.3)			94.0 (82.5-98.4)			88.0 (75.0-95.0)			68.0 (53.2-80.1)		
Status, n	3m			6m			12m			24m		
SQ tool	L	D	Total	L	D	Total	L	D	Total	L	D	Total
SQ+	159	18	177	140	37	177	122	55	177	77	100	177
SQ-	27	0	27	27	0	27	25	2	27	22	5	27
Total	186	18	204	167	37	204	147	57	204	99	105	204
Sensitivity, % and 95% CI	100 (78.1-100)			100 (88.3-100)			96.5 (86.8-99.4)			95.2 (88.7-98.2)		
Specificity, % and 95% CI	14.5 (9.9-20.6)			16.2 (11.1-22.8)			17.0 (11.5-24.3)			22.2 (14.7-31.9)		
Positive Predictive Value, % and 95% CI	10.2 (6.3-15.8)			20.9 (15.3-27.8)			31.0 (24.5-38.5)			56.5 (48.9-63.9)		
Negative Predictive Value, % and 95% CI	100 (84.5-100)			100 (84.5-100)			92.6 (74.2-98.7)			81.5 (61.3-93.0)		

Table 33. Sensitivity, specificity, and predictive values of NECPAL CCOMS-ICO© tool and SQ in nursing homes at 3, 6, 12 and 24 months (204 evaluable cases).
L indicates living; D: deceased.

III. Study III

The Cox model, a regression method for survival data, provides estimates of the hazard ratios, and their confidence intervals, of the explanatory variables. The hazard ratio is an estimate of the ratio of the hazard rate in the exposed versus the unexposed group. The hazard rate is the probability that if the event in question has not already occurred, it will occur in the next time interval, divided by the length of that interval. The time interval is made very short, so that in effect the hazard rate represents an instantaneous rate.

In this study, the hazard ratio indicates the relative risk of death in individuals with versus without an identified indicator at any given point in time, since an assumption of proportional hazards regression is that the hazard ratio is constant over time. This assumption of proportional hazards should always be tested.

For example, a hazard ratio of 2.0 for an identified indicator means that an individual presenting such indicator who has not yet died by a certain time has twice the chance of being dead at the next point in time compared to someone who does not present that indicator.

Identifying indicators associated with mortality within 24 months

A total of 388 individuals died during 2-year follow-up. A total of 1004 individuals were analysed. 59 observations were missing and, thus, deleted.

In the multivariate Cox model, identification of palliative care needs by healthcare professionals [hazard ratio (HR) 2.91, 95% confidence interval (CI) 2.24-3.79], infections with systemic impact (HR 2.23, 95% CI 1.50-3.30), and the surprise question (HR 2.09, 95% CI 1.45-3.01) were the indicators included in the NECPAL CCOMS-ICO© tool associated with a higher risk of mortality (Table 34). Some other indicators of advanced frailty, as severe dependency (HR 1.87, 95% CI 1.44-2.43), nutritional decline (HR 1.53, 95% CI 1.23-1.90) or

confusional syndrome (HR 1.44, 95% CI 1.11-1.87), were associated with a higher risk of mortality within 24 months after identification, as well as individualôs request for palliative care approach (HR 1.61, 95% CI 1.01-2.46). Co-morbidity (Charlson index, HR 1.12, 95% CI 1.07-1.18) and age (HR 1.02, 95% CI 1.01-1.03) were also associated with an increased risk of death.

	Coef	SE (coef)	p value	Exp (coef) HR	95,0% CI for Exp (coef) HR	
					Lower	Upper
NUTRITIONAL DECLINE	0.43	0.11	0.000126	1.53	1.23	1.90
PC NEED IDENTIFIED BY HEALTHCARE PROFESSIONALS	1.07	0.13	2.22e-15	2.91	2.24	3.79
AGE	0.02	0.01	0.001862	1.02	1.01	1.03
INFECTIONS WITH SYSTEMIC IMPACT	0.80	0.20	7.36e-05	2.23	1.50	3.30
SEVERE DEPENDENCY (BARTHEL<20)	0.63	0.13	2.75e-06	1.87	1.44	2.43
CONFUSIONAL SYNDROME	0.36	0.13	0.006822	1.44	1.11	1.87
INDIVIDUAL'S REQUEST FOR PC APPROACH	0.48	0.22	0.027202	1.61	1.01	2.46
CHARLSON INDEX	0.12	0.02	5.18e-07	1.12	1.07	1.18
SQ	0.74	0.19	7.40e-05	2.09	1.45	3.01

Table 34. Factors associated with mortality within 24 months in recruited individuals (n=1063 individuals).

Evaluating the proportionality of hazards in predictive model

The effect of ñidentification of palliative care needs by healthcare professionalsò and ñnutritional declineò were non proportional, meaning that the hazard ratio of these variables is time dependent (Table 35). In such cases, the estimated hazard ratio for these two covariates can be understood as óaverage effectô over observed

time points. There was no violation of the proportionality assumption for the rest of indicators.

	rho	chisq	p value
NUTRITIONAL DECLINE	-0.122	5.806	1.60e-02
PC NEED IDENTIFIED BY HEALTHCARE PROFESSIONALS	-0.184	12.065	5.14e-04
AGE	-0.001	0.001	9.79e-01
INFECTIONS WITH SYSTEMIC IMPACT	-0.064	1.616	2.04e-01
SEVERE DEPENDENCY (BARTHEL<20)	-0.030	0.370	5.43e-01
CONFUSIONAL SYNDROME	-0.083	2.866	9.05e-02
INDIVIDUAL REQUEST FOR PC APPROACH	-0.036	0.507	4.77e-01
CHARLSON INDEX	-0.014	0.076	7.82e-01
SQ	-0.016	0.105	7.46e-01
GLOBAL	NA	35.332	5.21e-05

Table 35. Proportional hazards evaluation.

Testing the time dependent covariates is equivalent to testing for a non-zero slope in a generalized linear regression of the scaled Schoenfeld residuals on increasing transformations of time. A non-zero slope is an indication of a violation of the proportional hazard assumption. Graphical method employing Schoenfeld residuals for ñidentification of palliative care needs by healthcare professionalsò and ñnutritional declineò indicators (Figures 28 and 29) show a decreasing trend until 6 months, with no trend over time after this time point. This might lead to the conclusion that proportional hazard assumption is violated for both indicators and effect or impact of these indicators might be changing over time.

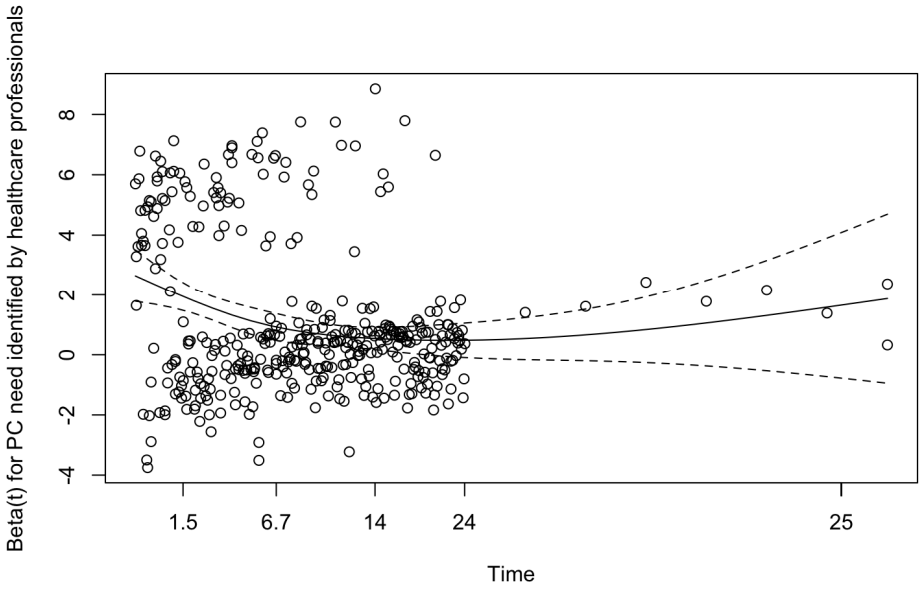

Figure 28. Plot of Schoenfeld residuals against transformed time: analysis of proportional hazard assumption verification for ñidentification of palliative care needs by healthcare professionalsò.

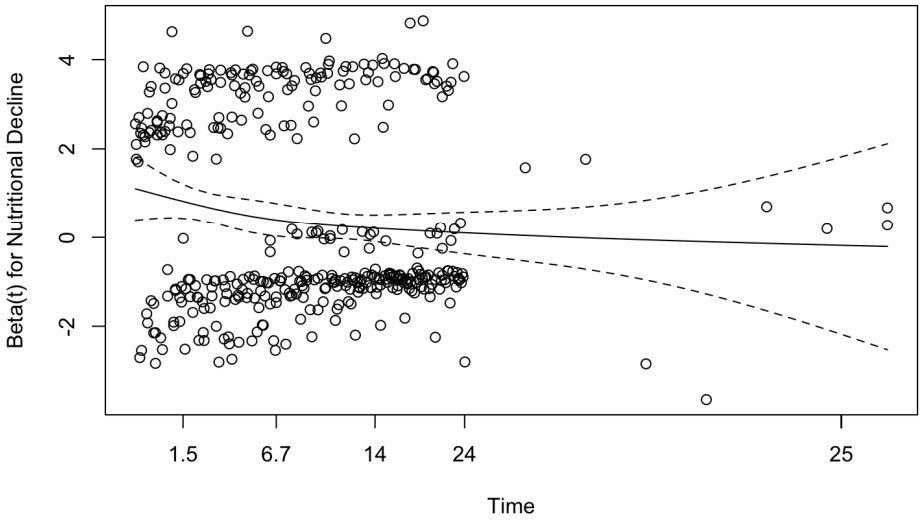

Figure 29. Plot of Schoenfeld residuals against transformed time: analysis of proportional hazard assumption verification for ñnutritional declineò.

As soon as it is stated that proportional hazard assumption is not satisfied for a covariate, and whether this changing impact is considered also of interest, it should be decided which approach is to be chosen in terms of Cox model construction and modification. There are two methods that are being considered most often: a) introducing interactions of selected covariates with function of time and b) stratification model.

Interaction with time

The first method uses interactions of the covariates for which proportional hazard assumption is not satisfied, ñidentification of palliative care needs by healthcare professionalsò and ñnutritional declineò, with a time transformation. We considered a unit step function with step at 6 months. Including this time transformation, we assumed proportional hazard ratios before and after 6 months for the two covariates.

The HR in the multivariate modified Cox model for ñidentification of palliative care needs by healthcare professionalsò before 6 months increases from 2.91 (95% CI 2.24-3.79) in the initial model to 4.78 (95% CI 3.36-6.80) (Table 36). Results are quite the opposite after 6 months: the coefficient for ñidentification of palliative care needs by healthcare professionalsò is 0.40 [Coef = 1.56 + (-1.16) = 0.40, SE (coef) = 0.23] and HR [Exp (coef)] is 1.5 (95% CI 0.96-2.35, p value = 0.078). As HR after 6 months is not statistically significant, the conclusion is that ñidentification of palliative care needs by healthcare professionalsò indicator increases the risk of death during the first 6 months, but not after this time point. In fact, after this time point, it is not a predictor of mortality.

Results are quite similar for ñnutritional declineò indicator. Before 6 months, HR increases from 1.53 (95% CI 1.23-1.90) in the initial model to 2.00 (95% CI 1.43-2.79). After 6 months, the coefficient for ñnutritional declineò is 0.21 [Coef = 0.69 + (-0.48) = 0.21, SE (coef) = 0.15] and HR [Exp (coef)] is 1.24 (95% CI 0.92-

1.66, p value = 0.159). The conclusion is the same, as HR after 6 months is not statistically significant, ñnutritional declineò indicator increases the risk of death during the first 6 months, but not after this time point. Therefore, after 6 months, ñnutritional declineò is not a predictor of mortality.

	Coef	SE (coef)	p value	Exp (coef)	95,0% CI for Exp (coef)	
					Lower	Upper
NUTRITIONAL DECLINE	0.69	0.17	4.64e-05	2.00	1.43	2.79
NUTRITIONAL DECLINE_t	-0.48	0.23	0.03345	0.62	0.40	0.96
PC NEED IDENTIFIED BY HEALTHCARE PROFESSIONALS	1.56	0.18	< 2e-16	4.78	3.36	6.80
PC NEED IDENTIFIED BY HEALTHCARE PROFESSIONALS_t	-1.16	0.29	4.88e-05	0.31	0.18	0.55
AGE	0.02	0.005	0.00157	1.02	1.01	1.03
INFECTIONS WITH SYSTEMIC IMPACT	0.81	0.20	6.55e-05	2.24	1.51	3.33
SEVERE DEPENDENCY (BARTHEL<20)	0.62	0.13	3.88e-06	1.86	1.43	2.41
CONFUSIONAL SYNDROME	0.37	0.13	0.00578	1.45	1.11	1.88
INDIVIDUAL'S REQUEST FOR PC APPROACH	0.43	0.22	0.04869	1.53	1.00	2.34
CHARLSON INDEX	0.11	0.02	4.11e-06	1.11	1.06	1.17
SQ	0.77	0.19	3.60e-05	2.16	1.50	3.10

Table 36. Multivariate modified Cox model, including interaction between the indicators ñidentification of palliative care needs by healthcare professionalsò and ñnutritional declineò and the unit step function at 6 months.

Regarding the rest of indicators associated with a higher risk of death -infections with systemic impact, the surprise question, severe dependency, nutritional decline, confusional syndrome, individualôs request for palliative care approach, co-morbidity and age- there are very discrete differences in the covariateôs influence on the hazard level between the initial model and the model adding

interactions with time, and HR of each indicator remains practically without modifications in the two models.

After adding interactions with time, for ñidentification of palliative care needs by healthcare professionalsò and ñnutritional declineò, the assumption of proportional hazards (statistical significance) is verified again (Table 37). As newly added variables turn out to be non-significant, it indicates that proportional hazard assumption is satisfied for the given covariates, which means that their effect is not changing over time.

	rho	chisq	p value
NUTRITIONAL DECLINE	-0.017	0.111	0.7395
NUTRITIONAL DECLINE_t	-0.016	0.104	0.7477
PC NEED IDENTIFIED BY HEALTHCARE PROFESSIONALS	-0.011	0.049	0.8256
PC NEED IDENTIFIED BY HEALTHCARE PROFESSIONALS_t	-0.032	0.387	0.5337
AGE	-0.003	0.003	0.9547
INFECTIONS WITH SYSTEMIC IMPACT	-0.063	1.591	0.2072
SEVERE DEPENDENCY (BARTHEL<20)	-0.035	0.499	0.4799
CONFUSIONAL SYNDROME	-0.086	3.063	0.0801
INDIVIDUAL REQUEST FOR PC APPROACH	-0.045	0.789	0.3744
CHARLSON INDEX	-0.016	0.111	0.7394
SQ	-0.018	0.136	0.7124
GLOBAL	NA	9.741	0.5538

Table 37. Proportional hazards evaluation in modified model (interactions with time).
ñIdentification of palliative care needs by healthcare professionalsò indicates before 6 months.
ñIdentification of palliative care needs by healthcare professionals_tò indicates after 6 months.
ñNutritional declineò indicates before 6 months.
ñNutritional decline_tò indicates after 6 months.

Stratified model

The second method that enables to handle non-proportional hazards is stratification. The main idea is to split the whole sample into subgroups on the basis of categorical variable which is called stratification variable and re-estimate the model, letting the baseline hazard function differ between these subgroups. In this case, stratification variables are ñidentification of palliative care needs by healthcare professionalsò (present vs absent) and ñnutritional declineò (present vs absent), resulting in the splitting of the whole sample into 4 subgroups.

It makes sense to choose a categorical covariate as a stratification variable if it interacts with time (i.e. proportional hazard assumption is not satisfied for this covariate) and is not of primary interest, as stratification of the model automatically excludes stratification variable from explanatory variables set (Table 38).

	Coef	SE (coef)	p value	Exp (coef) HR	95,0% CI for Exp (coef) HR	
					Lower	Upper
AGE	0.02	0.005	0.00147	1.02	1.01	1.03
INFECTIONS WITH SYSTEMIC IMPACT	0.78	0.20	0.00013	2.17	1.50	3.24
SEVERE DEPENDENCY (BARTHEL<20)	0.59	0.13	1.18e-05	1.80	1.39	2.35
CONFUSIONAL SYNDROME	0.35	0.13	0.00838	1.43	1.10	1.86
INDIVIDUAL'S REQUEST FOR PC APPROACH	0.41	0.22	0.05816	1.51	1.00	2.31
CHARLSON INDEX	0.10	0.02	9.38e-06	1.11	1.06	1.16
SQ	0.77	0.19	3.66e-05	2.16	1.50	3.11

Table 38. Multivariate modified Cox model, excluding stratification indicators ñidentification of palliative care needs by healthcare professionalsò and ñnutritional declineò from explanatory variables set.

As it can be noticed, hazard ratios for explanatory indicators do not differ to a large extent as compared with those in the initial model not stratified.

The assumption of proportional hazards (statistical significance) is verified again (Table 39), indicating that proportional hazard assumption is satisfied for all indicators, which means that their effect is not changing over time.

	rho	chisq	p value
AGE	-0.001	0.0002	0.989
INFECTIONS WITH SYSTEMIC IMPACT	-0.059	1.401	0.237
SEVERE DEPENDENCY (BARTHEL<20)	-0.047	0.916	0.339
CONFUSIONAL SYNDROME	-0.070	1.991	0.158
INDIVIDUAL REQUEST FOR PC APPROACH	-0.043	0.697	0.404
CHARLSON INDEX	-0.012	0.059	0.808
SQ	-0.022	0.202	0.653
GLOBAL	NA	4.887	0.674

Table 39. Proportional hazards evaluation in stratified model.

Evaluating predictive model

For practical application, the main product of a Cox model is a prognostic index. The ROC curve shows the possible combination of sensitivity and specificity for predicting the risk of death at different cut-off points of the prognostic index. For example, in the initial model, at 3 months a cut-off of 0.31 implies that individuals with an estimated score above this point were predicted to die within 3 months while those with a score equal to or below 0.31 were predicted to be alive. This classification successfully predicted 76% of all individuals who died (sensitivity) and 76% of all individuals who were alive (specificity) (Table 40).

To assess the modelôs discrimination ability to predict the risk of death at different time points, the AUC was measured at 3, 6, 12 and 24 months.

Living vs deceased n	Area under the curve (AUC)	Asymptotic 95% CI		Prognostic score	Sensibility	Specificity
		Lower Bound	Upper Bound			
3m (919 vs 85)	0.83	0.79	0.88	0.25	0.80	0.73
				0.31	0.76	0.76
				0.45	0.71	0.80
6m (854 vs 150)	0.82	0.79	0.86	0.13	0.80	0.69
				0.25	0.75	0.76
				0.35	0.69	0.80
12m (743 vs 261)	0.77	0.74	0.81	-0.11	0.80	0.57
				0.09	0.70	0.71
				0.27	0.60	0.80
24m (625 vs 379)	0.74	0.71	0.77	-0.25	0.80	0.50
				-0.01	0.67	0.66
				0.24	0.53	0.80

Table 40. Modelôs discrimination ability.

The AUC was progressively decreasing through time, from excellent discrimination at 3 and 6 months (0.83 (95% CI 0.79-0.88) and 0.82 (95% CI 0.79-0.86, respectively) to acceptable discrimination at 12 and 24 months (0.77 (95% CI 0.74-0.81) and 0.74 (95% CI 0.71-0.77, respectively) (Figure 30). At 3, 6 and 12 months, highest concurrent sensitivity and specificity were above 70%.

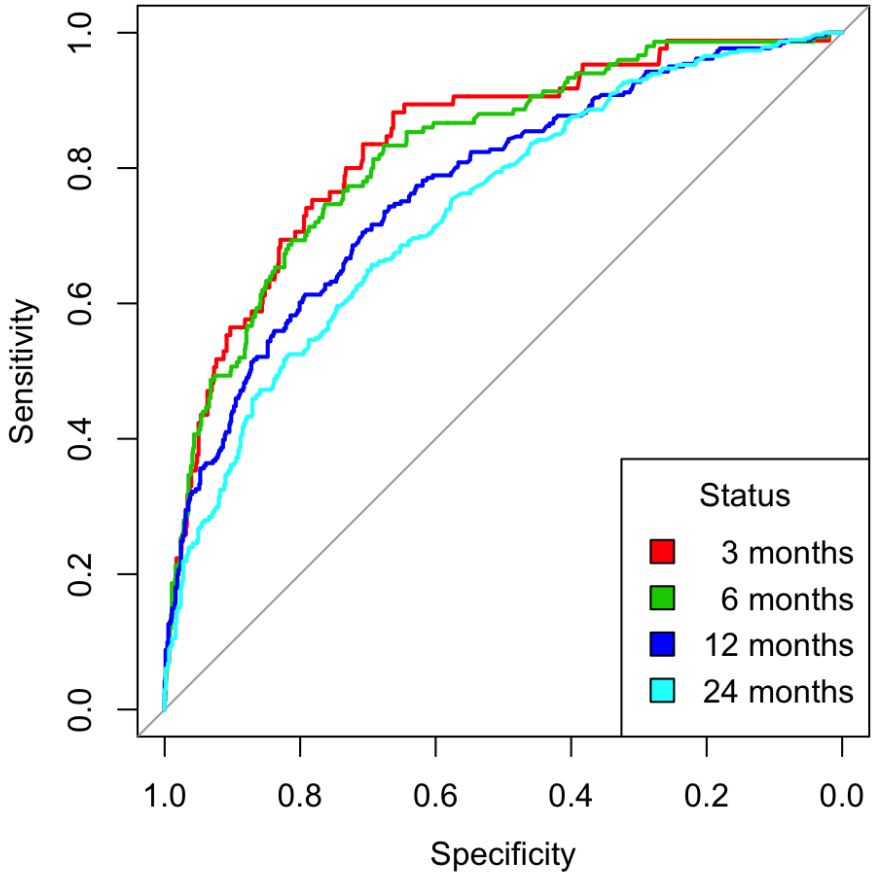

Figure 30. Evaluation of the ability to predict death within 3, 6, 12 and 24 months. Results expressed by the receiver operating characteristic (ROC) curve.

Nevertheless, it should be taken into account that hazard ratios for two covariates in the model (ñidentification of palliative care needs by healthcare professionalsò and ñnutritional declineò) were time dependent. Explanation of hazard ratio óaverage effectô may probably have affected the modelôs discrimination before and after 6 months.

It could not be rejected that the variation of the effect through time of these two time dependent indicators were related to heterogeneity of studied sample. Anyway, stratification model importantly pointed it out. As stratification of the

model automatically excluded stratification indicators from explanatory variables set and both indicators, ñidentification of palliative care needs by healthcare professionalsò and ñnutritional declineò, were of primary interest, an alternative approach consisting of splitting the whole sample into potentially more homogeneous subgroups, was explored and is presented below.

Exploring identification of factors associated with mortality and development of predictive models per condition

Cancer

A total of 72 individuals died during 2-year follow-up. A total of 105 individuals were analysed. 3 observations were missing and, thus, deleted.

In the multivariate Cox model, identification of palliative care needs by healthcare professionals (HR 3.38, 95% CI 1.87-6.11), carerôs request for palliative care approach (HR 1.98, 95% CI 1.11-3.55), and severe emotional distress (HR 1.71, 95% CI 1.01-2.92) were the only indicators included in the NECPAL CCOMS-ICO© tool associated with a higher risk of mortality among individuals with cancer (Table 41).

	Coef	SE (coef)	p value	Exp (coef) HR	95,0% CI for Exp (coef) HR	
					Lower	Upper
PC NEED IDENTIFIED BY HEALTHCARE PROFESSIONALS	**1.22**	**0.30**	**5.57e-05**	**3.38**	**1.87**	**6.11**
SEVERE EMOTIONAL DISTRESS	**0.54**	**0.27**	**0.0479**	**1.71**	**1.01**	**2.92**
CARER'S REQUEST FOR PC APPROACH	**0.68**	**0.30**	**0.0216**	**1.98**	**1.11**	**3.55**

Table 41. Factors associated with mortality within 24 months in recruited individuals with cancer (n=108 individuals).

There was no violation of the proportionality assumption for any of the indicators associated with mortality within 24 months in recruited individuals with cancer, meaning that their hazard ratio were constant over time (Table 42).

	rho	chisq	p value
PC NEED IDENTIFIED BY HEALTHCARE PROFESSIONALS	**-0.081**	**0.583**	**0.445**
SEVERE EMOTIONAL DISTRESS	**0.102**	**0.758**	**0.384**
CARER'S REQUEST FOR PC APPROACH	**0.050**	**0.227**	**0.634**
GLOBAL	**NA**	**1.557**	**0.669**

Table 42. Proportional hazards evaluation in cancer.

The AUC was progressively increasing through time, from acceptable discrimination at 3 and 6 months (0.71 (95% CI 0.61-0.82) and 0.78 (95% CI 0.69-0.87, respectively), with highest concurrent sensitivity and specificity above 70%, to excellent discrimination at 12 months [0.86 (95% CI 0.79-0.93)] and highest concurrent sensitivity and specificity above 80%. At 24 months, the modelôs discrimination is acceptable [0.80 (95% CI 0.73-0.88)] and highest concurrent sensitivity and specificity is above 70% (Table 43 and Figure 31).

Living vs deceased n	Area under the curve (AUC)	Asymptotic 95% CI		Prognostic score	Sensibility	Specificity
		Lower Bound	Upper Bound			
3m (73 vs 32)	0.71	0.61	0.82	-0.52	0.78	0.52
				-0.18	0.72	0.66
				0.43	0.50	0.81
6m (56 vs 49)	0.78	0.69	0.87	-0.52	0.82	0.64
				-0.18	0.73	0.79
				-0.18	0.73	0.79
12m (40 vs 65)	0.86	0.79	0.93	-0.52	0.82	0.83
				-0.52	0.82	0.83
				-0.18	0.69	0.93
24m (33 vs 72)	0.80	0.73	0.88	-0.52	0.74	0.79
				-0.52	0.74	0.79
				-0.18	0.63	0.91

Table 43. Modelôs discrimination ability in cancer.

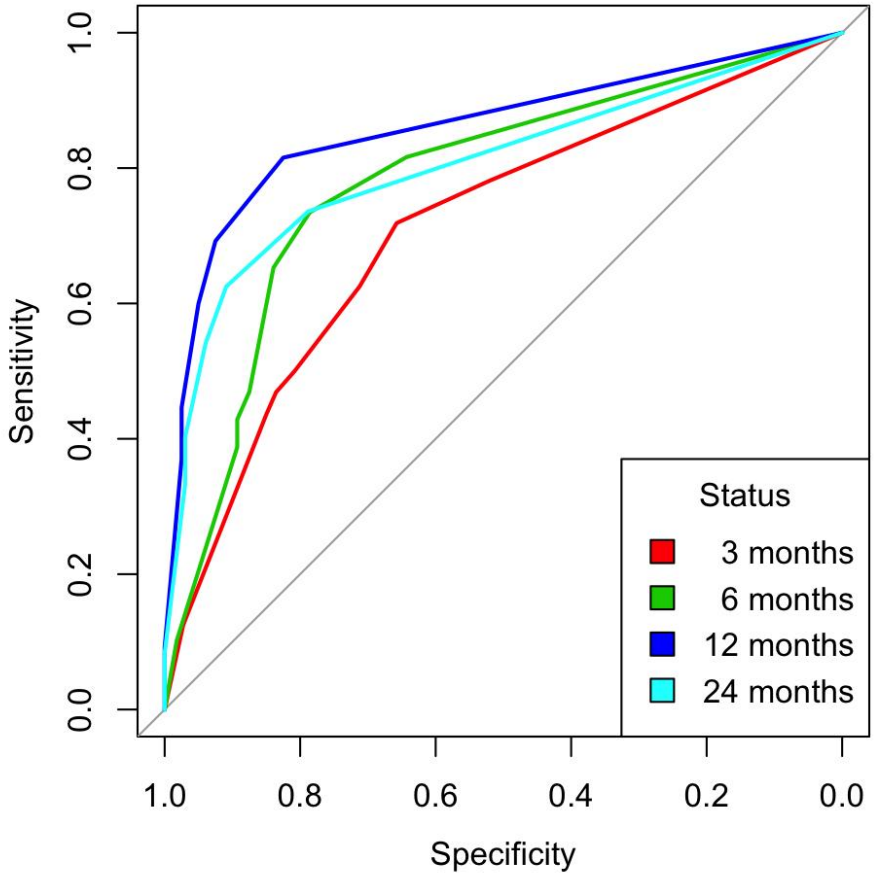

Figure 31. Evaluation of the ability to predict death within 3, 6, 12 and 24 months in cancer. Results expressed by the receiver operating characteristic (ROC) curve.

Dementia

A total of 110 individuals died during 2-year follow-up. A total of 200 individuals were analysed. 4 observations were missing and, thus, deleted.

In the multivariate Cox model, identification of palliative care needs by healthcare professionals (HR 2.46, 95% CI 1.46-4.15) and pressure sores GIII-IV (HR 2.34, 95% CI 1.28-4.29) were the only indicators included in the NECPAL CCOMS-ICO© tool associated with a higher risk of mortality within 24 months among individuals with dementia (Table 44).

	Coef	SE (coef)	p value	Exp (coef) HR	95,0% CI for Exp (coef) HR	
					Lower	Upper
PC NEED IDENTIFIED BY HEALTHCARE PROFESSIONALS	**0.90**	**0.27**	**0.000701**	**2.46**	**1.46**	**4.15**
PRESSURE SORES GIII-IV	**0.85**	**0.31**	**0.005742**	**2.34**	**1.28**	**4.29**

Table 44. Factors associated with mortality within 24 months in recruited individuals with dementia (n=204 individuals).

There was no violation of the proportionality assumption for any of the indicators associated with mortality within 24 months in recruited individuals with dementia, meaning that their hazard ratio were constant over time (Table 45).

	rho	chisq	p value
PC NEED IDENTIFIED BY HEALTHCARE PROFESSIONALS	**-0.113**	**1.365**	**0.243**
PRESSURE SORES GIII-IV	**-0.004**	**0.002**	**0.964**
GLOBAL	**NA**	**1.365**	**0.505**

Table 45. Proportional hazards evaluation in dementia.

Nevertheless, the model failed to discriminate between individuals with a risk to die or to be alive at any time point analysed, with AUC below 0.60 at 3, 6, 12 and 24 months (Table 46 and Figure 32).

Living vs deceased n	Area under the curve (AUC)	Asymptotic 95% CI		Prognostic score	Sensibility	Specificity
		Lower Bound	Upper Bound			
3m (185 vs 15)	0.57	0.44	0.70	NA	NA	NA
				0.71	0.27	0.90
				0.26	0.27	0.84
6m (163 vs 37)	0.56	0.48	0.64	NA	NA	NA
				0.71	0.22	0.91
				0.26	0.24	0.85
12m (132 vs 68)	0.59	0.53	0.65	NA	NA	NA
				0.26	0.28	0.89
				0.71	0.22	0.95
24m (92 vs 108)	0.57	0.52	0.62	NA	NA	NA
				0.26	0.23	0.91
				0.71	0.16	0.95

Table 46. Modelôs discrimination ability in dementia.

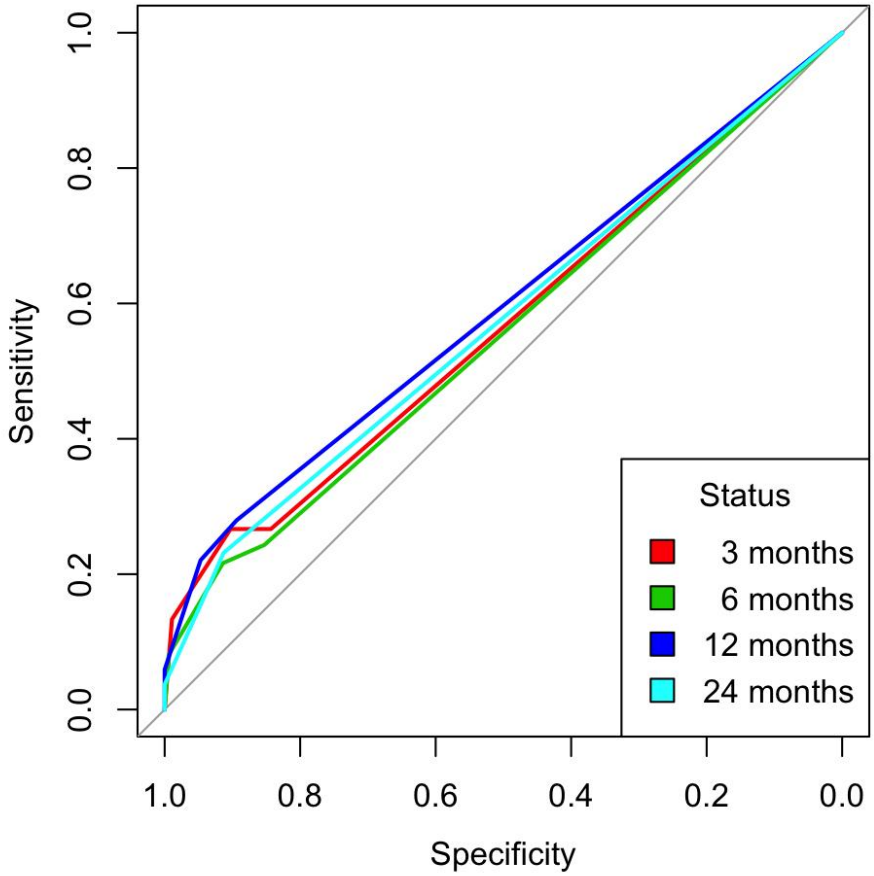

Figure 32. Evaluation of the ability to predict death within 3, 6, 12 and 24 months in dementia. Results expressed by the receiver operating characteristic (ROC) curve.

Advanced frailty

A total of 98 individuals died during 2-year follow-up. A total of 374 individuals were analysed. 33 observations were missing and, thus, deleted.

In the multivariate Cox model, infections with systemic impact (HR 4.11, 95% CI 1.68-10.01), confusional syndrome (HR 2.73, 95% CI 1.71-4.36), identification of palliative care needs by healthcare professionals (HR 2.70, 95% CI 1.33-5.52) and complex/intense nursing care needs (HR 2.35, 95% CI 1.36-4.06) were the indicators included in the NECPAL CCOMS-ICO© tool associated with a higher risk of mortality (Table 47). Some other indicators, as falls (HR 1.95, 95% CI 1.08-3.50), co-morbidity (Charlson index, HR 1.16, 95% CI 1.05-1.27), urgent admissions (HR 1.11, 95% CI 1.01-1.23) and age (HR 1.05, 95% CI 1.02-1.09) were also associated with an increased risk of death within 24 months after identification.

	Coef	SE (coef)	p value	Exp (coef) HR	95,0% CI for Exp (coef) HR	
					Lower	Upper
FALLS	0.67	0.30	0.02628	1.95	1.08	3.50
PC NEED IDENTIFIED BY HEALTHCARE PROFESSIONALS	1.00	0.36	0.00623	2.70	1.33	5.52
AGE	0.05	0.02	0.00234	1.05	1.02	1.09
INFECTIONS WITH SYSTEMIC IMPACT	1.41	0.45	0.00189	4.11	1.68	10.01
COMPLEX/INTENSIVE NURSING CARE NEEDS	0.85	0.28	0.00215	2.35	1.36	4.06
URGENT ADMISSIONS	0.11	0.05	0.03478	1.11	1.01	1.23
CONFUSIONAL SYNDROME	1.01	0.24	2.45e-05	2.73	1.71	4.36
CHARLSON INDEX	0.15	0.05	0.00291	1.16	1.05	1.27

Table 47. Factors associated with mortality within 24 months in recruited individuals with advanced frailty (n=407 individuals).

There was no violation of the proportionality assumption for any of the indicators associated with mortality within 24 months in recruited individuals with advanced frailty, meaning that their hazard ratio were constant over time (Table 48).

	rho	chisq	p value
FALLS	**-0.061**	**0.351**	**0.554**
PC NEED IDENTIFIED BY HEALTHCARE PROFESSIONALS	**-0.141**	**1.826**	**0.177**
AGE	**0.047**	**0.254**	**0.614**
INFECTIONS WITH SYSTEMIC IMPACT	**-0.064**	**0.381**	**0.537**
COMPLEX/INTENSIVE NURSING CARE NEEDS	**-0.090**	**0.699**	**0.403**
URGENT ADMISSIONS	**-0.064**	**0.486**	**0.486**
CONFUSIONAL SYNDROME	**0.028**	**0.072**	**0.789**
CHARLSON INDEX	**-0.049**	**0.222**	**0.637**
GLOBAL	**NA**	**6.284**	**0.615**

Table 48. Proportional hazards evaluation in advanced frailty.

The AUC was progressively decreasing through time, from outstanding discrimination at 3 months [0.92 (95% CI 0.85-0.99)], with highest concurrent sensitivity and specificity above 80%, to acceptable discrimination at 6, 12 and 24 months [0.79 (95% CI 0.70-0.87), 0.73 (95% CI 0.65-0.81) and 0.72 (95% CI 0.66-0.78), respectively] (Table 49 and Figure 33). At 6 and 12 months, highest concurrent sensitivity and specificity were above 70%, decreasing below this threshold only at 24 months.

Living vs deceased n	Area under the curve (AUC)	Asymptotic 95% CI		Prognostic score	Sensibility	Specificity
		Lower Bound	Upper Bound			
3m (357 vs 17)	0.92	0.85	0.99	0.66	0.82	0.86
				0.66	0.82	0.86
				0.45	0.82	0.81
6m (341 vs 33)	0.79	0.70	0.87	-0.21	0.82	0.52
				0.15	0.73	0.73
				0.41	0.58	0.80
12m (314 vs 60)	0.73	0.65	0.81	-0.31	0.80	0.46
				0.06	0.70	0.71
				0.31	0.55	0.80
24m (280 vs 94)	0.72	0.66	0.78	-0.34	0.81	0.48
				-0.04	0.66	0.67
				0.22	0.51	0.80

Table 49. Modelôs discrimination ability in advanced frailty.

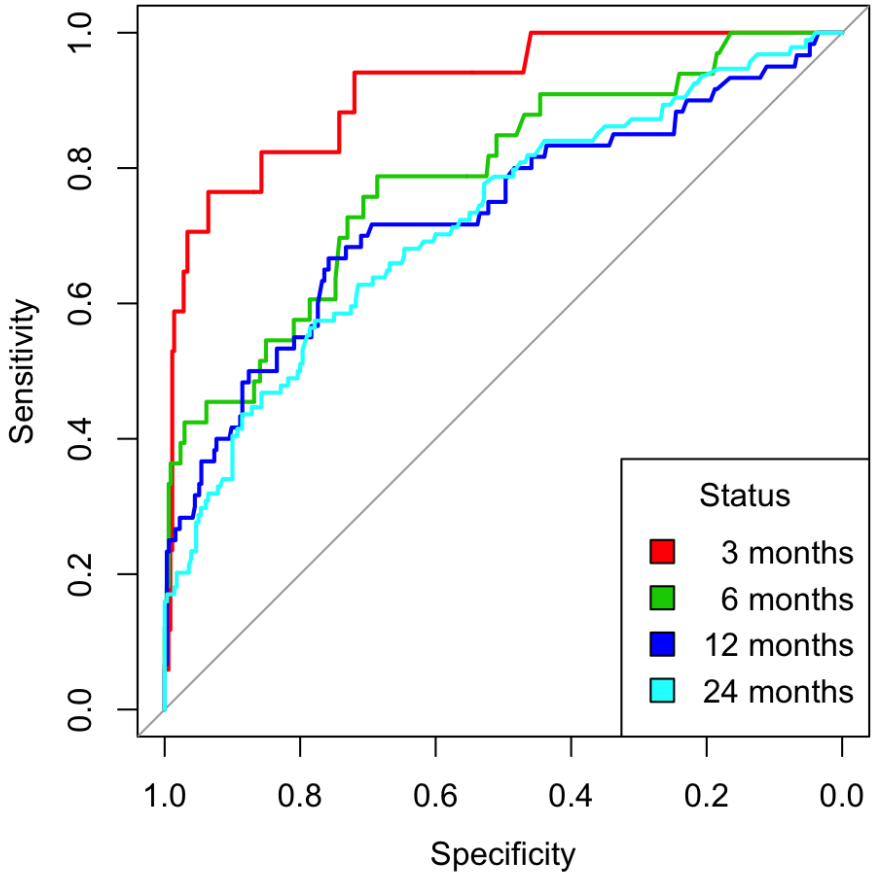

Figure 33. Evaluation of the ability to predict death within 3, 6, 12 and 24 months in advanced frailty. Results expressed by the receiver operating characteristic (ROC) curve.

Organ failure

A total of 109 individuals died during 2-year follow-up. A total of 312 individuals were analysed. 32 observations were missing and, thus, deleted.

In the multivariate Cox model, the surprise question (HR 3.07, 95% CI 1.54-6.15), infections with systemic impact (HR 2.96, 95% CI 1.66-5.26) and carerôs request for palliative care approach (HR 2.31, 95% CI 1.47-3.61) were the indicators included in the NECPAL CCOMS-ICO© tool associated with a higher risk of mortality (Table 50). Some other indicators, as falls (HR 1.99, 95% CI 1.03-3.86), severe dependency (HR 1.87, 95% CI 1.07-3.27), confusional syndrome (HR 1.74, 95% CI 1.07-2.83), complex/intense nursing care needs (HR 1.69, 95% CI 1.08-2.65) and age (HR 1.02, 95% CI 1.003-1.04) were also associated with an increased risk of death within 24 months after identification.

This is the only condition where identification of palliative care needs by healthcare professionals does not appear as an indicator associated with mortality within 24 months, and also the only one where the surprise question does, associated, moreover, with the highest risk of mortality.

	Coef	SE (coef)	p value	Exp (coef) HR	95,0% CI for Exp (coef) HR	
					Lower	Upper
FALLS	0.69	0.34	0.040444	1.99	1.03	3.86
AGE	0.02	0.01	0.019636	1.02	1.003	1.04
INFECTIONS WITH SYSTEMIC IMPACT	1.08	0.29	0.000223	2.96	1.66	5.26
SEVERE DEPENDENCY (BARTHEL<20)	0.63	0.29	0.027864	1.87	1.07	3.27
COMPLEX/INTENSIVE NURSING CARE NEEDS	0.53	0.23	0.022261	1.69	1.08	2.65
CONFUSIONAL SYNDROME	0.55	0.25	0.025830	1.74	1.07	2.83
CARER'S REQUEST FOR PC APPROACH	0.84	0.23	0.000270	2.31	1.47	3.61
SQ	1.12	0.35	0.001486	3.07	1.54	6.15

Table 50. Factors associated with mortality within 24 months in recruited individuals with organ failure (n=344 individuals).

There was no violation of the proportionality assumption for any of the indicators associated with mortality within 24 months in recruited individuals with organ failure, meaning that their hazard ratio were constant over time (Table 51).

	rho	chisq	p value
FALLS	-0.173	3.465	0.063
AGE	0.149	2.421	0.120
INFECTIONS WITH SYSTEMIC IMPACT	-0.061	0.418	0.518
SEVERE DEPENDENCY (BARTHEL<20)	-0.028	0.088	0.767
COMPLEX/INTENSIVE NURSING CARE NEEDS	-0.109	1.386	0.239
CONFUSIONAL SYNDROME	-0.130	1.704	0.192
CARER'S REQUEST FOR PC APPROACH	-0.087	0.811	0.368
SQ	-0.094	0.981	0.322
GLOBAL	NA	10.530	0.230

Table 51. Proportional hazards evaluation in organ failure.

The AUC was progressively decreasing through time until 12 months, from excellent discrimination at 3 months [0.81 (95% CI 0.71-0.91)], with highest concurrent sensitivity and specificity around 70%, to acceptable discrimination at 6 and 12 [0.79 (95% CI 0.70-0.88) and 0.74 (95% CI 0.67-0.81), respectively], with a slightly increase in the AUC at 24 months [0.75 (95% CI 0.69-0.80) (Table 52 and Figure 34). At 6 and 24 months, highest concurrent sensitivity and specificity were around 70%. The modelôs discrimination ability showed its worse AUC, sensitivity and specificity at 12 months.

Living vs deceased n	Area under the curve (AUC)	Asymptotic 95% CI		Prognostic score	Sensibility	Specificity
		Lower Bound	Upper Bound			
3m (289 vs 23)	0.81	0.71	0.91	0.03	0.83	0.61
				0.27	0.74	0.69
				0.63	0.65	0.81
6m (278 vs 34)	0.79	0.70	0.88	-0.04	0.82	0.56
				0.27	0.74	0.71
				0.59	0.65	0.80
12m (241 vs 71)	0.74	0.67	0.81	-0.14	0.80	0.52
				0.03	0.68	0.66
				0.52	0.55	0.80
24m (206 vs 106)	0.75	0.69	0.80	-0.14	0.80	0.57
				-0.02	0.70	0.67
				0.44	0.49	0.80

Table 52. Modelôs discrimination ability in organ failure.

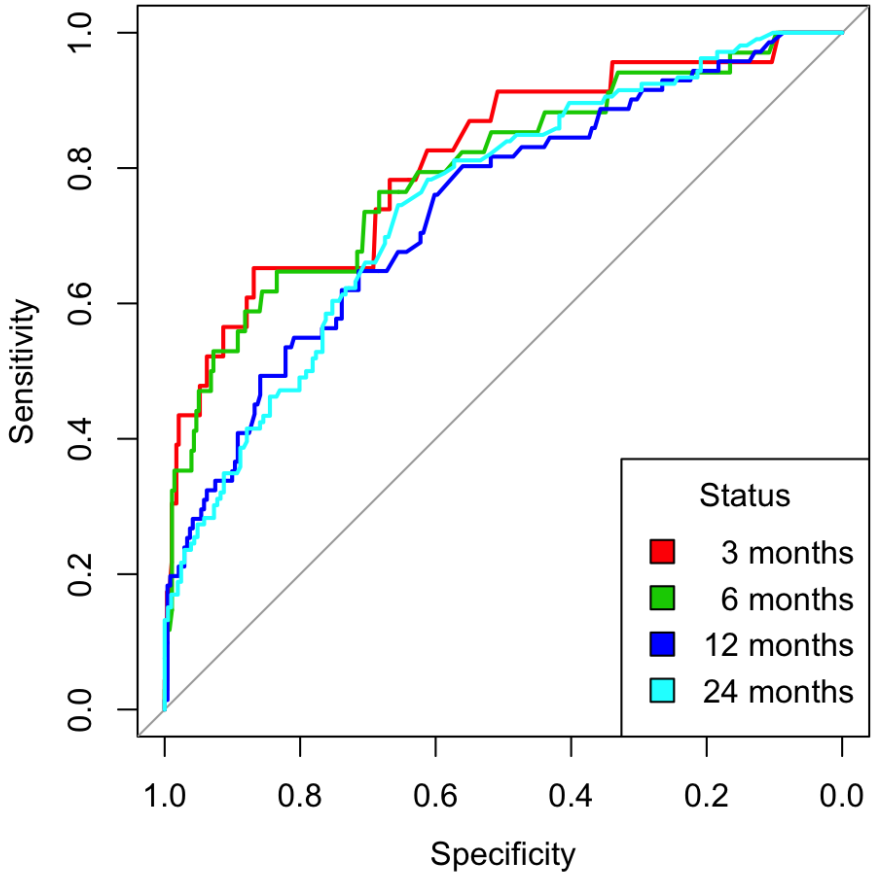

Figure 34. Evaluation of the ability to predict death within 3, 6, 12 and 24 months in organ failure. Results expressed by the receiver operating characteristic (ROC) curve.

A summary of factors associated with mortality within 24 months in recruited individuals and per condition is shown in Table 53.

HR	COHORT	CANCER	DEMENTIA	ADVANCED FRAILTY	ORGAN FAILURE
NUTRITIONAL DECLINE	1.53				
PC NEED IDENTIFIED BY HEALTHCARE PROFESSIONALS	2.91	3.38	2.46	2.70	
AGE	1.02			1.05	1.02
COMPLEX/INTENSIVE NURSING CARE NEEDS				2.35	1.69
INFECTIONS WITH SYSTEMIC IMPACT	2.23			4.11	2.96
FALLS				1.95	1.99
SEVERE DEPENDENCY (BARTHEL<20)	1.87				1.87
CONFUSIONAL SYNDROME	1.44			2.73	1.74
PRESSURE SORES GIII-IV			2.34		
SEVERE EMOTIONAL DISTRESS		1.71			
INDIVIDUAL'S REQUEST FOR PC APPROACH	1.61				
CARER'S REQUEST FOR PC APPROACH		1.98			2.31
URGENT ADMISSIONS				1.11	
CHARLSON INDEX	1.12			1.16	
SQ	2.09				3.07

Table 53. Summary table showing the hazard ratio (HR) of factors associated with mortality within 24 months in recruited individuals (cohort) and per condition.

Exploring identification of factors associated with mortality and development of predictive models per setting of care

Primary care centres

A total of 208 individuals died during 2-year follow-up. A total of 667 individuals were analysed. 64 observations were missing and, thus, deleted.

In the multivariate Cox model, identification of palliative care needs by healthcare professionals (HR 2.97, 95% CI 2.03-4.33) and the surprise question (HR 2.07, 95% CI 1.33-3.24) were the indicators included in the NECPAL CCOMS-ICO© tool associated with a higher risk of mortality within 24 months among individuals recruited from primary care centres (Table 54). Some other indicators, as severe dependency (HR 1.83, 95% CI 1.23-2.72), complex/intensive nursing care needs (HR 1.68, 95% CI 1.21-2.33), nutritional decline (HR 1.39, 95% CI 1.02-1.91), urgent admissions (HR 1.27, 95% CI 1.13-1.42), co-morbidity (Charlson index, HR 1.10, 95% CI 1.04-1.18) and age (HR 1.03, 95% CI 1.01-1.04) were associated with a higher risk of mortality within 24 months after identification.

	Coef	SE (coef)	p value	Exp (coef) HR	95,0% CI for Exp (coef) HR	
					Lower	Upper
NUTRITIONAL DECLINE	0.33	0.16	0.036856	1.39	1.02	1.91
PC NEED IDENTIFIED BY HEALTHCARE PROFESSIONALS	1.09	0.19	1.64e-08	2.97	2.03	4.33
AGE	0.03	0.01	0.000201	1.03	1.01	1.04
SEVERE DEPENDENCY (BARTHEL<20)	0.60	0.20	0.002993	1.83	1.23	2.72
COMPLEX/INTENSIVE NURSING CARE NEEDS	0.52	0.17	0.001769	1.68	1.21	2.33
URGENT ADMISSIONS	0.24	0.06	4.15e-05	1.27	1.13	1.42
CHARLSON INDEX	0.10	0.03	0.002406	1.10	1.04	1.18
SQ	0.73	0.23	0.001358	2.07	1.33	3.24

Table 54. Factors associated with mortality within 24 months in individuals recruited from primary care centres (n=731 individuals).

The effect of ñidentification of palliative care needs by healthcare professionalsò was non proportional, meaning that it was a time dependent covariate (Table 55). In such case, hazard ratio for this covariate can be understood as ǿaverage effectô over observed time points. There was no violation of the proportionality assumption for the rest of indicators.

Graphical method employing Schoenfeld residuals for ñidentification of palliative care needs by healthcare professionalsò indicator (Figure 35) show a decreasing trend until approximately 6 months, with no trend over time after this time point. This might lead to the conclusion that proportional hazard assumption is violated for this indicator and its effect might be changing over time.

	rho	chisq	p value
NUTRITIONAL DECLINE	-0.116	3.149	0.0760
PC NEED IDENTIFIED BY HEALTHCARE PROFESSIONALS	-0.166	5.826	0.0158
AGE	0.017	0.071	0.7895
SEVERE DEPENDENCY (BARTHEL<20)	-0.083	1.508	0.2195
COMPLEX/INTENSIVE NURSING CARE NEEDS	0.036	0.295	0.5871
URGENT ADMISSIONS	-0.083	1.423	0.2329
CHARLSON INDEX	0.008	0.014	0.9058
SQ	0.015	0.046	0.8309
GLOBAL	NA	16.566	0.0350

Table 55. Proportional hazards evaluation in primary care centres.

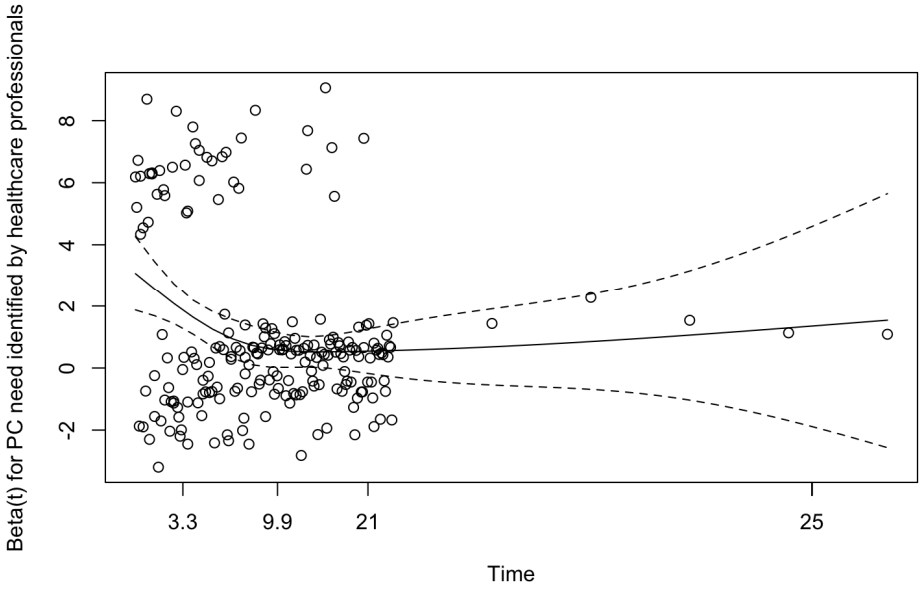

Figure 35. Plot of Schoenfeld residuals against transformed time: analysis of proportional hazard assumption verification for ñidentification of palliative care needs by healthcare professionalsò in primary care centres.

The AUC was progressively decreasing through time, from excellent discrimination at 3 and 6 months (0.85 (95% CI 0.78-0.92) and 0.82 (95% CI 0.76-0.87, respectively) to acceptable discrimination at 12 and 24 months (0.74 (95% CI 0.70-0.79) and 0.73 (95% CI 0.69-0.77, respectively) (Table 56 and Figure 36). For 3 and 6 months, highest concurrent sensitivity and specificity were above 70%. At 12 and 24 months, highest concurrent sensitivity and specificity slightly decreased and were around 70%.

Living vs deceased n	Area under the curve (AUC)	Asymptotic 95% CI		Prognostic score	Sensibility	Specificity
		Lower Bound	Upper Bound			
3m (633 vs 34)	0.85	0.78	0.92	0.36	0.82	0.76
				0.36	0.79	0.76
				0.48	0.76	0.80
6m (596 vs 71)	0.82	0.76	0.87	0.23	0.80	0.73
				0.29	0.76	0.75
				0.41	0.68	0.80
12m (524 vs 143)	0.74	0.70	0.79	-0.16	0.80	0.47
				0.12	0.70	0.69
				0.36	0.54	0.80
24m (465 vs 202)	0.73	0.69	0.77	-0.19	0.80	0.47
				0.06	0.67	0.68
				0.28	0.54	0.80

Table 56. Modelôs discrimination ability in primary care centres.

Nevertheless, modelôs discrimination ability should be considered with caution, taken into account that hazard ratio for one covariate in the model (ñidentification of palliative care needs by healthcare professionalsò) was time dependent. Explanation of hazard ratio óaverage effectô would probably affect the modelôs discrimination approximately before and after 6 months.

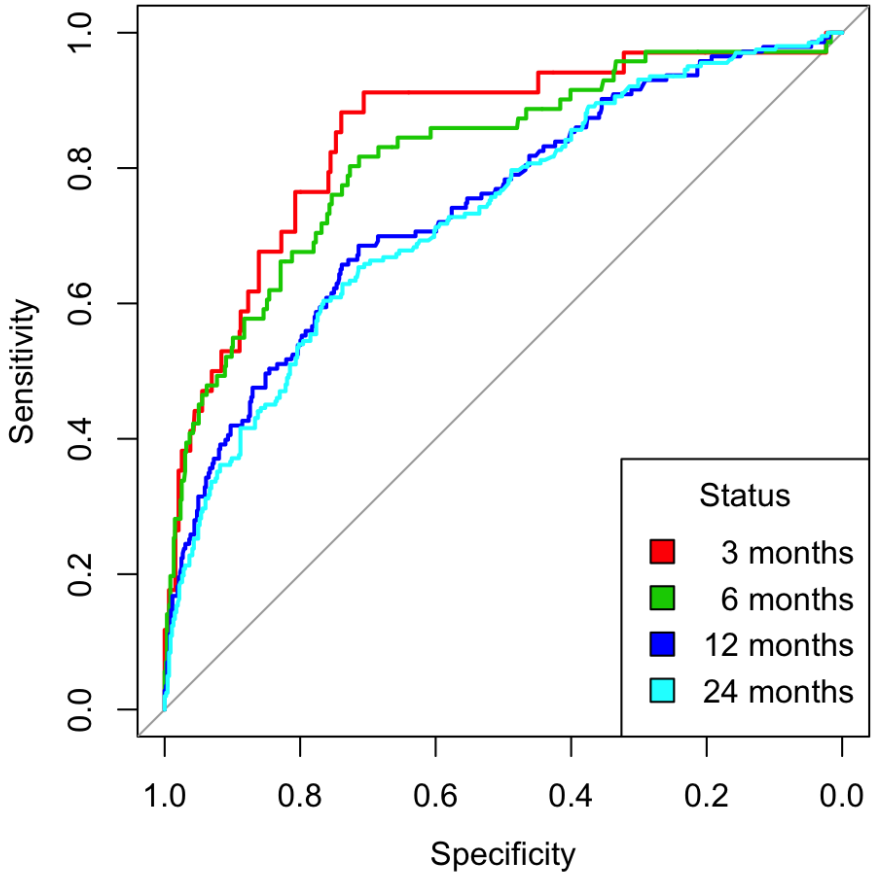

Figure 36. Evaluation of the ability to predict death within 3, 6, 12 and 24 months in primary care centres. Results expressed by the receiver operating characteristic (ROC) curve.

Intermediate care centre

A total of 40 individuals died during 2-year follow-up. A total of 69 individuals were analysed. 5 observations were missing and, thus, deleted.

In the multivariate Cox model, individualôs request for palliative care approach (HR 8.79, 95% CI 3.49-22.11), nutritional decline (HR 4.02, 95% CI 2.03-7.93), functional decline (HR 2.67, 95% CI 1.32-5.41) and co-morbidity (Charlson index, HR 1.13, 95% CI 1.02-1.25) were the only indicators included in the NECPAL CCOMS-ICO© tool associated with a higher risk of mortality within 24 months among individuals recruited from intermediate care centre (Table 57).

	coef	SE (coef)	p value	Exp (coef) HR	95,0% CI for Exp (coef) HR	
					Lower	Upper
NUTRITIONAL DECLINE	1.39	0.35	6.26e-05	4.02	2.03	7.93
FUNCTIONAL DECLINE	0.98	0.36	0.00639	2.67	1.32	5.41
INDIVIDUAL'S REQUEST FOR PC APPROACH	2.17	0.47	3.88e-06	8.79	3.49	22.11
CHARLSON INDEX	0.12	0.05	0.01540	1.13	1.02	1.25

Table 57. Factors associated with mortality within 24 months in individuals recruited from intermediate care centre (n=74 individuals).

The effect of ñnutritional declineò was non proportional, meaning that it was a time dependent covariate (Table 58) and hazard ratio for this covariate should be understood as óaverage effectô over observed time points. There was no violation of the proportionality assumption for the rest of indicators.

	rho	chisq	p value
NUTRITIONAL DECLINE	**-0.351**	**4.080**	**0.0434**
FUNCTIONAL DECLINE	**-0.188**	**1.392**	**0.2381**
INDIVIDUAL'S REQUEST FOR PC APPROACH	**0.085**	**0.285**	**0.5936**
CHARLSON INDEX	**0.277**	**2.978**	**0.0844**
GLOBAL	**NA**	**7.510**	**0.1113**

Table 58. Proportional hazards evaluation in intermediate care centre.

Graphical method employing Schoenfeld residuals for ñnutritional declineò indicator (Figure 37) show a decreasing trend over time. This might lead to the conclusion that proportional hazard assumption is violated for this indicator and its effect might be changing over time.

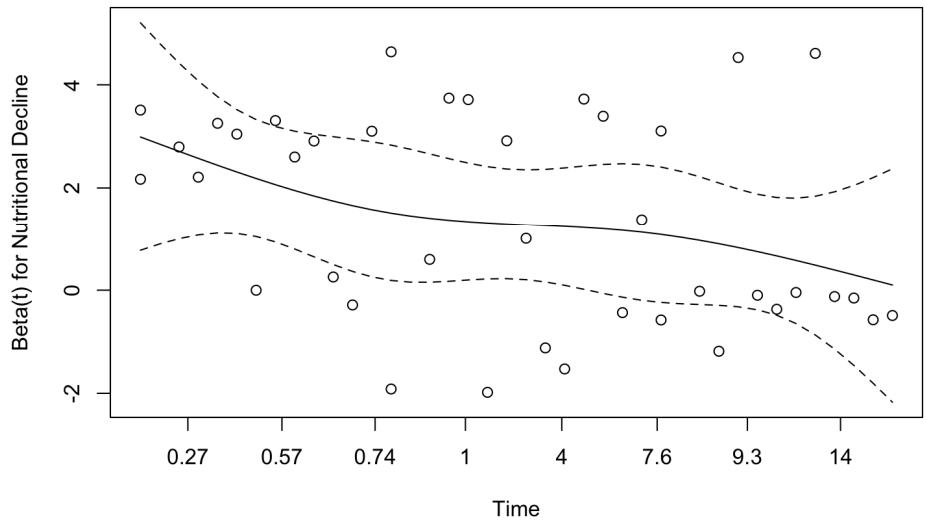

Figure 37. Plot of Schoenfeld residuals against transformed time: analysis of proportional hazard assumption verification for ñnutritional declineò in intermediate care centre.

At any observed time point, the modelôs discrimination is excellent [0.90 (95% CI 0.83-0.97) at 3 months, 0.90 (95% CI 0.83-0.98) at 6 months, 0.90 (95% CI 0.83-0.97) at 12 months and 0.89 (95% CI 0.82-0.96) at 24 months] (Table 59 and Figure 38). At 3 and 6 months, highest concurrent sensitivity and specificity were above 80%. At 12 and 24 months, highest concurrent sensitivity and specificity slightly decreased and were around 80%.

Living vs deceased n	Area under the curve (AUC)	Asymptotic 95% CI		Prognostic score	Sensibility	Specificity
		Lower Bound	Upper Bound			
3m (50 vs 19)	0.90	0.83	0.97	0.92	0.84	0.88
				0.86	0.89	0.88
				0.26	0.89	0.80
6m (45 vs 24)	0.90	0.83	0.98	0.26	0.83	0.84
				0.26	0.83	0.84
				0.16	0.83	0.80
12m (34 vs 35)	0.90	0.83	0.97	-0.37	0.80	0.76
				-0.0007	0.77	0.82
				-0.0007	0.77	0.82
24m (29 vs 40)	0.89	0.82	0.96	-0.50	0.80	0.72
				-0.43	0.78	0.79
				-0.19	0.73	0.83

Table 59. Modelôs discrimination ability in intermediate care centre.

Nevertheless, modelôs discrimination ability should be considered with caution, taken into account that hazard ratio for one covariate in the model (ñnutritional declineò) was time dependent. Explanation of hazard ratio óaverage effectô would probably affect the modelôs discrimination.

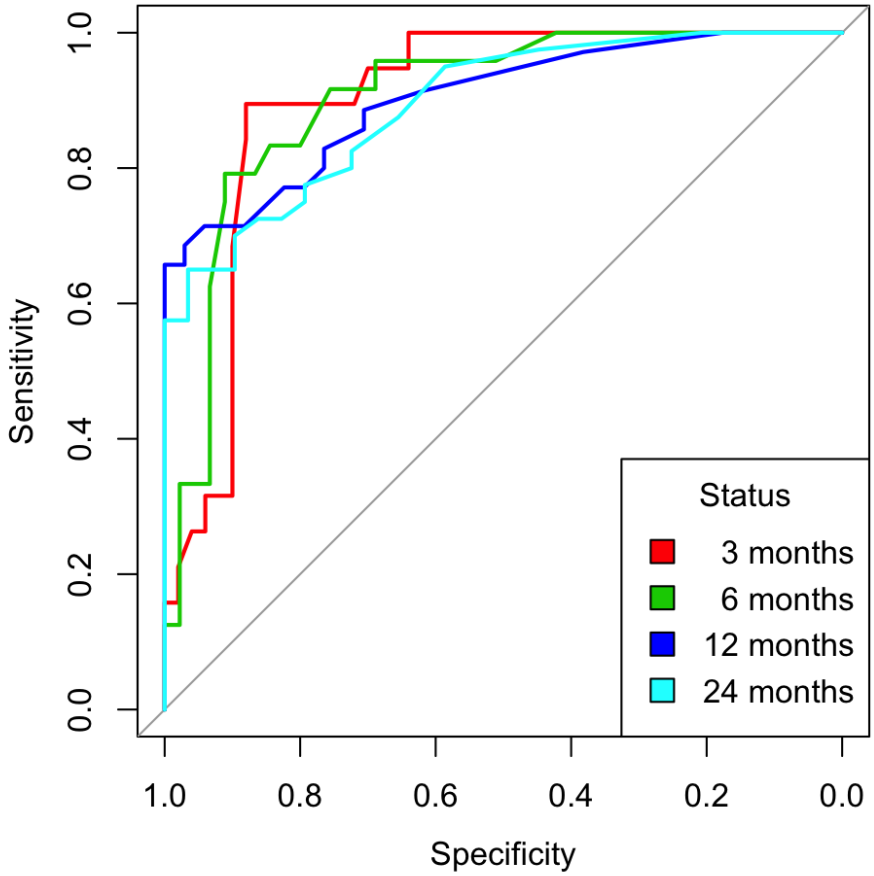

Figure 38. Evaluation of the ability to predict death within 3, 6, 12 and 24 months in intermediate care centre. Results expressed by the receiver operating characteristic (ROC) curve.

Acute bed hospital

A total of 30 individuals died during 2-year follow-up. A total of 53 individuals were analysed. 1 observation was missing and, thus, deleted.

In the multivariate Cox model, pressure sores GIII-IV (HR 21.17, 95% CI 2.24-199.67), severe dependency (HR 11.23, 95% CI 2.02-62.44), nutritional decline (HR 4.25, 95% CI 1.90-9.53), male gender (HR 2.78, 95% CI 1.22-6.30) and functional decline (HR 2.86, 95% CI 1.28-6.41) were the indicators included in the NECPAL CCOMS-ICO© tool associated with a higher risk of mortality within 24 months among individuals recruited from acute bed hospital (Table 60).

	coef	SE (coef)	p value	Exp (coef) HR	95,0% CI for Exp (coef) HR	
					Lower	Upper
NUTRITIONAL DECLINE	1.45	0.41	0.000435	4.25	1.90	9.53
MALE GENDER	1.02	0.42	0.014566	2.78	1.22	6.30
FUNCTIONAL DECLINE	1.052	0.41	0.010641	2.86	1.28	6.41
SEVERE DEPENDENCY (BARTHEL<20)	2.42	0.88	0.005709	11.23	2.02	62.44
PRESSURE SORES GIII-IV	3.05	1.15	0.007684	21.17	2.24	199.67

Table 60. Factors associated with mortality within 24 months in individuals recruited from acute bed hospital (n=54 individuals).

The effect of ñfunctional declineò was non proportional, meaning that it was a time dependent covariate (Table 61) and hazard ratio for this covariate should be understood as óaverage effectô over observed time points. There was no violation of the proportionality assumption for the rest of indicators.

	rho	Chisq	p value
NUTRITIONAL DECLINE	-0.368	3.163	0.0753
MALE GENDER	-0.165	0.693	0.4050
FUNCTIONAL DECLINE	0.429	7.463	0.0063
SEVERE DEPENDENCY (BARTHEL<20)	-0.229	1.496	0.2213
PRESSURE SORES GIII-IV	0.116	0.396	0.5291
GLOBAL	NA	10.708	0.0575

Table 61. Proportional hazards evaluation in acute bed hospital.

Graphical method employing Schoenfeld residuals for ñfunctional declineò indicator (Figure 39) show an increasing trend over time. This might lead to the conclusion that proportional hazard assumption is violated for this indicator and its effect might be changing over time.

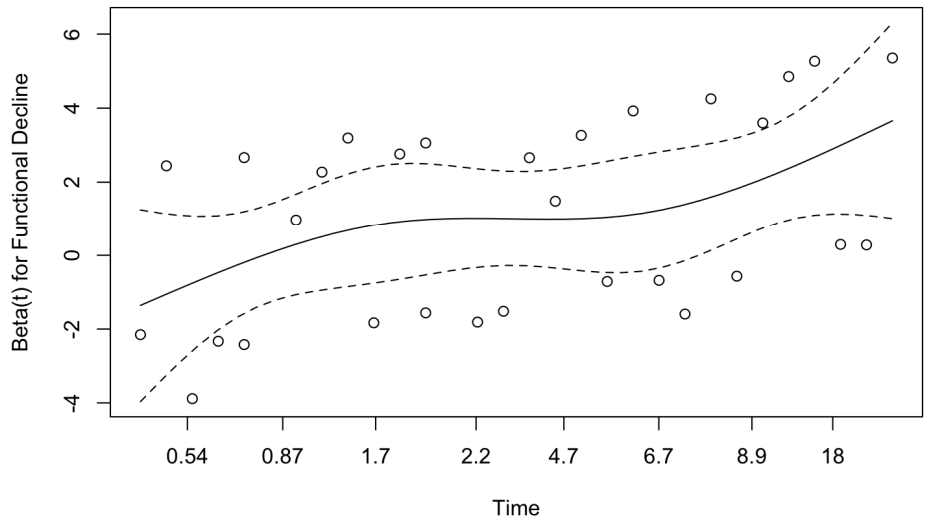

Figure 39. Plot of Schoenfeld residuals against transformed time: analysis of proportional hazard assumption verification for ñfunctional declineò in acute bed hospital.

At any observed time point, the modelôs discrimination is excellent [0.82 (95% CI 0.70-0.95) at 3 months, 0.87 (95% CI 0.77-0.97) at 6 months, 0.88 (95% CI 0.79-0.96) at 12 months and 0.84 (95% CI 0.74-0.94) at 24 months] (Table 62 and Figure 40). At 3 and 6 months, highest concurrent sensitivity and specificity were around 80%. At 12 and 24 months, highest concurrent sensitivity and specificity slightly decreased and were around 70%.

Living vs deceased n	Area under the curve (AUC)	Asymptotic 95% CI		Prognostic score	Sensibility	Specificity
		Lower Bound	Upper Bound			
3m (38 vs 15)	0.82	0.70	0.95	0.28	0.80	0.79
				0.28	0.80	0.79
				0.76	0.73	0.87
6m (33 vs 20)	0.87	0.77	0.97	-0.45	0.80	0.67
				0.28	0.75	0.85
				0.28	0.75	0.85
12m (27 vs 26)	0.88	0.79	0.96	-0.45	0.78	0.74
				-0.45	0.77	0.74
				-0.23	0.73	0.85
24m (23 vs 30)	0.84	0.74	0.94	-0.45	0.73	0.78
				-0.45	0.73	0.78
				-0.23	0.67	0.87

Table 62. Modelôs discrimination ability in acute bed hospital.

Nevertheless, modelôs discrimination ability should be considered with caution, taken into account that hazard ratio for one covariate in the model (ñfunctional declineò) was time dependent. Explanation of hazard ratio óaverage effectô would probably affect the modelôs discrimination.

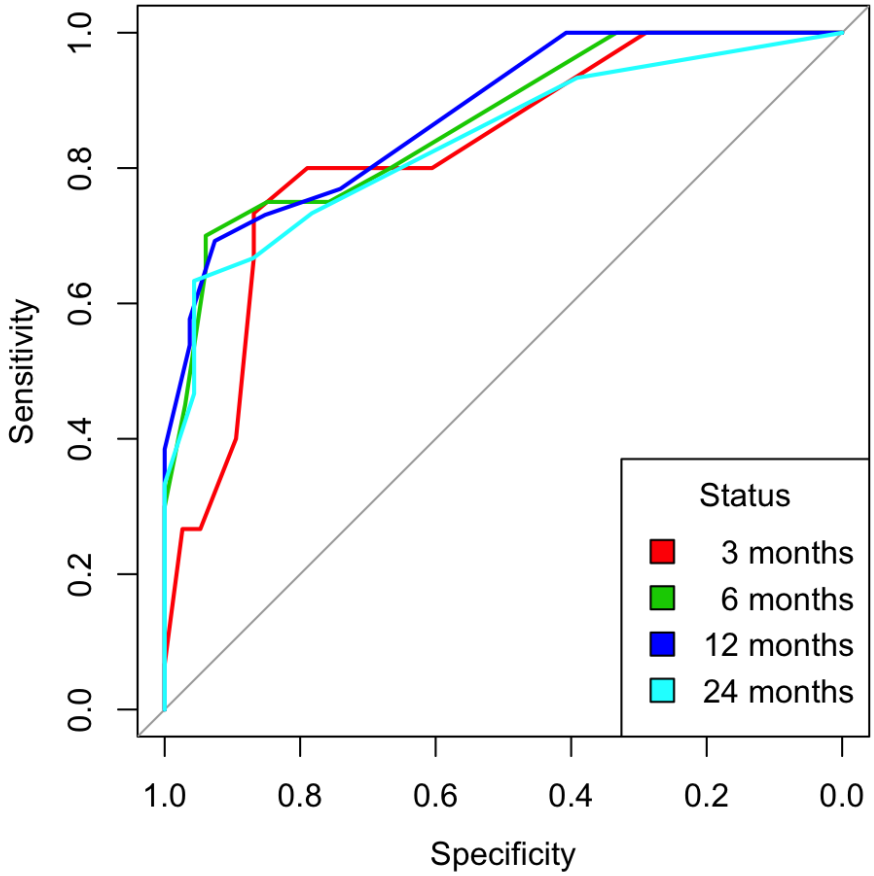

Figure 40. Evaluation of the ability to predict death within 3, 6, 12 and 24 months in acute bed hospital. Results expressed by the receiver operating characteristic (ROC) curve.

Nursing homes

A total of 106 individuals died during 2-year follow-up. A total of 201 individuals were analysed. 3 observations were missing and, thus, deleted.

In the multivariate Cox model, identification of palliative care needs by healthcare professionals (HR 17.65, 95% CI 7.07-44.04), the surprise question (HR 3.48, 95% CI 1.41-8.62) and pressure sores GIII-IV (HR 2.73, 95% CI 1.35-5.53) were the indicators included in the NECPAL CCOMS-ICO© tool associated with a higher risk of mortality within 24 months among individuals recruited from nursing homes (Table 63). Some other indicators, as confusional syndrome (HR 1.80, 95% CI 1.03-3.12) and age (HR 1.03, 95% CI 1.01-1.06) were associated with a higher risk of mortality within 24 months after identification. It is remarkable the effect of complexe/intensive nursing care needs, as its presence was associated with a lower risk of mortality within 24 months among individuals recruited from nursing homes (HR 0.21, 95% CI 0.06-0.76).

	Coef	SE (coef)	p value	Exp (coef) HR	95,0% CI for Exp (coef) HR	
					Lower	Upper
PC NEED IDENTIFIED BY HEALTHCARE PROFESSIONALS	2.87	0.47	7.59e-10	17.65	7.07	44.04
AGE	0.03	0.01	0.00922	1.03	1.01	1.06
COMPLEX/INTENSIVE NURSING CARE NEEDS	-1.57	0.66	0.01796	0.21	0.06	0.76
CONFUSIONAL SYNDROME	0.59	0.28	0.03786	1.80	1.03	3.12
PRESSURE SORES GIII-IV	1.00	0.36	0.00532	2.73	1.35	5.53
SQ	1.25	0.46	0.00694	3.48	1.41	8.62

Table 63. Factors associated with mortality within 24 months in individuals recruited from nursing homes (n=204 individuals).

There was no violation of the proportionality assumption for any of the indicators associated with mortality within 24 months in individuals recruited from nursing homes, meaning that their hazard ratio were constant over time (Table 64).

	rho	chisq	p value
PC NEED IDENTIFIED BY HEALTHCARE PROFESSIONALS	**-0.009**	**0.010**	**0.919**
AGE	**-0.130**	**1.347**	**0.246**
COMPLEX/INTENSIVE NURSING CARE NEEDS	**-0.008**	**0.008**	**0.928**
CONFUSIONAL SYNDROME	**0.007**	**0.006**	**0.941**
PRESSURE SORES GIII-IV	**0.051**	**0.280**	**0.596**
SQ	**-0.056**	**0.328**	**0.567**
GLOBAL	**NA**	**2.089**	**0.911**

Table 64. Proportional hazards evaluation in nursing homes.

Nevertheless, the model was poor discriminating between individuals with a risk to die or to be alive at 3, 6 and 12 months, with AUC below 0.70 (Table 65 and Figure 41). Only at 24 months the AUC showed acceptable discrimination, although highest concurrent sensitivity and specificity was around 60%.

Living vs deceased n	Area under the curve (AUC)	Asymptotic 95% CI		Prognostic score	Sensibility	Specificity
		Lower Bound	Upper Bound			
3m (184 vs 17)	0.66	0.52	0.79	-0.11	0.82	0.40
				0.09	0.59	0.63
				0.32	0.35	0.80
6m (165 vs 36)	0.68	0.59	0.77	-0.11	0.81	0.42
				0.06	0.61	0.61
				0.26	0.36	0.81
12m (146 vs 55)	0.68	0.59	0.76	-0.15	0.82	0.40
				0.02	0.58	0.58
				0.23	0.40	0.82
24m (98 vs 103)	0.70	0.63	0.77	-0.15	0.82	0.51
				-0.01	0.64	0.64
				0.19	0.37	0.82

Table 65. Modelôs discrimination ability in nursing homes.

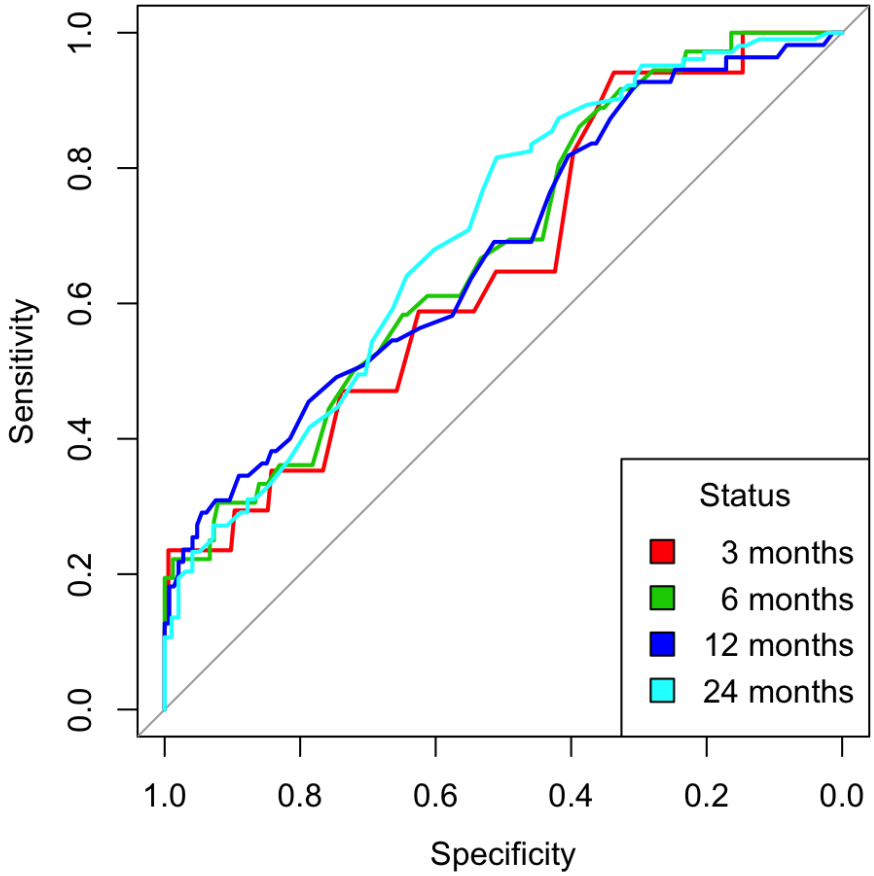

Figure 41. Evaluation of the ability to predict death within 3, 6, 12 and 24 months in nursing homes. Results expressed by the receiver operating characteristic (ROC) curve.

A summary of factors associated with mortality within 24 months in recruited individuals and per setting of care is shown in Table 66.

HR	COHORT	PRIMARY CARE	INTERMED CARE	ACUTE HOSPITAL	NURSING HOMES
NUTRITIONAL DECLINE	1.53	1.39	4.02	4.25	
FUNCTIONAL DECLINE			2.67	2.86	
PC NEED IDENTIFIED BY HEALTHCARE PROFESSIONALS	2.91	2.97			17.65
AGE	1.02	1.03			1.03
MALE GENDER				2.78	
COMPLEX/INTENSIVE NURSING CARE NEEDS		1.68			0.21 (-)
INFECTIONS WITH SYSTEMIC IMPACT	2.23				
SEVERE DEPENDENCY (BARTHEL<20)	1.87	1.83		11.23	
CONFUSIONAL SYNDROME	1.44				1.80
PRESSURE SORES GIII-IV				21.17	2.73
INDIVIDUAL'S REQUEST FOR PC APPROACH	1.61		8.79		
URGENT ADMISSIONS		1.27			
CHARLSON INDEX	1.12	1.10	1.13		
SQ	2.09	2.07			3.48

Table 66. Summary table showing the hazard ratio (HR) of factors associated with mortality within 24 months in recruited individuals (cohort) and per setting of care.

IX. General discussion

The overall aim of this thesis was to evaluate the usefulness of the NECPAL CCOMS-ICO© tool in identifying individuals with advanced chronic conditions who may benefit from an early palliative care approach, through employing it as a tool to determine the population-based prevalence of these individuals *(Study I)*, evaluating its predictive validity for mortality at 3, 6, 12 and 24 months to inform usefulness as screening tool for early palliative care *(Study II)* and identifying the indicators that were associated with mortality within 24 months to develop a predictive model for identifying individuals at high risk of death *(Study III)*.

Population-based prevalence

The population-based prevalence of individuals with advanced chronic conditions who may benefit from an early palliative care approach has been determined for the first time in a district, together with their characteristics and setting of care, employing one of the existing available tools to identify those individuals who may require such care: the NECPAL CCOMS-ICO© tool.

This prospective approach constitutes an innovative assessment of the population-based needs for palliative care. Methodologies based on retrospective assessments from causes of death, can also provide valid estimates.[104 105 106 107 108 109 110 111] Nevertheless, they are not useful for improving clinical practice, as they do not allow to identify patients in clinical settings, while this innovative approach is potentially transferable to the clinical practice and allows prospective identification.

NECPAL+ individuals are mainly among the elderly population. They live at home and nursing homes, although high prevalence is observed in intermediate care centre and acute bed hospital. Organ failure and advanced frailty are the most

common conditions they present, followed by dementia and cancer. There are higher proportions of women and non-cancer patients. These findings are consistent with previous published estimations.[120] [94] Physicians and nurses identify different groups of individuals with advanced chronic conditions who may benefit from an early palliative care approach.

The groups of individuals identified as SQ+ and NECPAL+ are nested groups and they are, essentially, the same population. Differences between these groups are attributable to differences observed among individuals with organ failure and advanced frailty conditions, as well as among individuals recruited in primary care centres and nursing homes. These findings would point out the higher severity presented by individuals identified as NECPAL+ with dementia and cancer, confirmed by the highest frequencies of disease-specific indicators of severity and progression presented by individuals with these two conditions, and also among those identified in acute bed hospital and intermediate care centre, consistently reflecting the kind of population, more seriously ill, expected to be attended to in these settings of care.

As almost all SQ+ individuals presented, at least, one additional NECPAL CCOMS-ICO© toolôs positive indicator, an additional interpretation based on these findings would suggest that scant differences exist between SQ+ identification and NECPAL+ identification, as currently defined, and that it does not improve the performance of the SQ in identifying patients likely in need of palliative care. Thus, according to this evidence, it would be questionable the recommendation of its use.

In the same way, almost all identified individuals with advanced chronic conditions who may benefit from an early palliative care approach, regardless of condition, presented some positive general clinical indicator of severity and progression from category 3 of the NECPAL CCOMS-ICO© tool. This suggests the importance of these kind of indicators and of this innovative approach, based on the accumulation of deficits to define severe advanced frailty, to identify this

population.[121 122] Other available tools, such as PIG[90] and SPICT,[21] are mainly based on Fried criteria[123] and, thus, designed to identify moderate frailty at an early stage (shrinking, weakness, poor endurance, slowness, and low activity). In the NECPAL CCOMS-ICO© tool, four of six domains within this high prevalent category correspond to deficits caused by severe advanced frailty, encompassing geriatric syndromes (with increasing evidence as an independent prognostic marker),[124] use of resources and nutritional and functional decline, both considered as dynamic as well as static variables. These general clinical indicators of severity and progression are not usually registered in mortality registries, which usually record individual diseases. This innovative approach jointly with high proportion of elderly people in studied County would explain high prevalence found.

Moreover, a broad majority of NECPAL+ individuals presented co-morbidities, making clear that multimorbidity is the most common condition among the elderly people.[14 125] The majority presence of general clinical indicators of severity and progression, regardless of condition, among identified individuals with advanced chronic conditions who may benefit from an early palliative care approach would suggest that disease-specific approach in an exclusive way may not be the most suitable one to identify this population.

Only in one-quarter of identified individuals, a request for palliative care approach or limitations to the use of major therapeutic interventions was made by individualsô carer. The frequency of requests made by individuals themselves is quite lower, which highlights the paternalistic pattern within the Spanish cultural context.[126]

One of the most significant findings from this study is the lack of concordance between physicians and nurses regarding the identification of individuals likely in need of palliative care. There was a moderate degree of agreement, with different populations being identified as SQ+, showing differences in their prediction of mortality before 12 months among recruited individuals. This low level of

concurrence between medical and nursing staff is consistent with available evidence.[127] [128] Consensus of definition and standardised validated criteria for the identification of individuals in need of palliative care are needed and could contribute to improve concordance between physicians and nurses.

Additionally, medical and nursing staff judged that a minority of the individuals they expected to die within 12 months was in need of a palliative care approach, suggesting that this needed approach might be related to recognition by healthcare professionals of transition 2 and indication of traditional palliative care more than to recognition of transition 1 and indication of early palliative care.[129] These findings would emphasize the need to reinforce the spreading of conceptual transitions in palliative care, systematically screen for palliative care needs in all target sub-populations and the importance of a multi-disciplinary approach.

Individualôs characteristics per condition and setting of care show that older women with advanced frailty and dementia are often based in home and nursing homes, while younger individuals suffering from organ failure and cancer are majority in acute bed hospital and intermediate care centre, as could be expected, which might be related to their current needs, the presence (or not) of primary carers, and required resources for their care. Nevertheless, it is important to point out that most identified individuals with advanced chronic conditions who may benefit from an early palliative care approach are community-dwelling people, except individuals with dementia, mainly based in nursing homes.

The consistent and systematic use of the NECPAL CCOMS-ICO© tool across all participating clinical settings showed that identification of these individuals is feasible and can be performed in any setting of care in daily clinical practice via multi-disciplinary assessment.

Predictive validity as screening tool

Among the existing available tools to identify individuals with advanced chronic conditions who may benefit from an early palliative care approach, the NECPAL CCOMS-ICO© tool has been the first one to be evaluated to determine its predictive validity for mortality to inform usefulness as screening tool for early palliative care from a population-based perspective.

The NECPAL CCOMS-ICO© tool and the SQ may be used, with a reasonable degree of accuracy, to screen individuals for early palliative care to ameliorate end-of-life suffering related to advanced chronic conditions. They present high sensitivity and high NPV at 3, 6, 12 and 24 months, an important finding given the consequences of failing to identify this vulnerable and often undetected and under-treated population. From a pragmatic approach, these screening tools provide early identification of patients that present a higher risk of death, thus enabling early assessment and delivery of early palliative care in individuals who screen positive and, effectively, present unmet palliative care needs.

Without screening, palliative care intervention would occur, if happened, throughout transition 2. However, end of life begins long before death becomes impending, and there is a period at which transition 1 might be detected by a screening tool. It is expected that recognition of transition 1 would lead to earlier palliative care intervention and that this, in turn, would lead to better outcomes. Although, this evidence is not yet available.

According to characteristics that a good screening test should present, the NECPAL CCOMS-ICO© tool is inexpensive, easy to administer, cause minimal (none) discomfort and is valid, as it distinguishes between individuals who will die and will not die. Significantly different mortality rates between NECPAL+ and NECPAL- populations and increased risk of death for those with positive identification would partially prove this validity.

Nevertheless, construct validity of the tool has been just partially explored by comparisons of mortality rates and calculation of risk ratios. Additional analysis regarding construct validity, such as internal consistency (which would assess the consistency of results across the items of the tool for addressing a unified construct) and reliability, the last characteristic that a good screening test should present (consistency in results with repeated measures, particularly inter-observer and intra-observer variability), remain unexplored and further research will be needed to better evaluate construct validity of the tool.

The criterion validity of the NECPAL CCOMS-ICO© tool has been explored by evaluating its predictive validity. The validity of the NECPAL CCOMS-ICO© tool as screening test is based, precisely, on its predictive validity for mortality, that is to say on its accuracy in identifying individuals who will die and will not die. Predictive validity can only be determined if the accuracy of the screening test can be compared to some "gold standard" that establishes the true status. In this study the gold standard is death, determined by following the participating individuals for a period of 24 months to determine which of them ultimately died. If the NECPAL CCOMS-ICO© tool were an ideal screening test, it would be exquisitely sensitive (high probability of detecting individuals who will die) and extremely specific (high probability that those that will not die will screen negative). But this is not the case.

The NECPAL CCOMS-ICO© tool presents high sensitivity, which is extremely convenient for screening purposes, but low specificity at 3, 6, 12 and 24 months. The probability of the NECPAL CCOMS-ICO© tool correctly identifying individuals who will not die was lower than 35% at any time point, that is to say there is a high proportion of false positives, individuals who test positive even though they really will not die, never lower than 65%, a consequence to screening that should need to be properly addressed.[130] As some of the individuals identified will end up living for years in a fragile state, although some others will die soon, all typically need the services that are priorities in the last part of life: advance

care planning, comfort measures, assistance for daily activities, family support, and so forth.[81]

NECPAL+ identification relies on the SQ, an estimation of mortality made by healthcare professionals and, as far as is known, human prediction on its own is fraught with bias.[49] Overestimation of survival has been reported when clinicians have been asked to predict it.[45] In the same way, an overestimation of mortality is observed when they are asked to predict it, as SQ does, a circumstance which could explain high proportion of false positives identified. Additionally, scant differences exist between SQ+ population and NECPAL+ population, as 93% of SQ+ individuals were also NECPAL+ individuals. This is the reason that would explain why predictive validity of the SQ is practically equal to predictive validity that has been calculated for the NECPAL CCOMS-ICO© tool. In light on this results, and as has been seen when identifying patients likely in need of palliative care with the SQ, the recommendation of its use would be questionable. Consequently, criterion of positivity should be reviewed to improve the predictive validity for mortality of the NECPAL CCOMS-ICO© tool.[131]

There are other aspects of predictive validity for mortality that should also be considered: the negative and positive predictive values. In this study, NPV is the probability that individuals with a negative screening test ultimately don't die, and PPV is the probability that individuals with a positive screening test ultimately die. One factor that influences the feasibility or the success of a screening program is the yield, i.e., the number of cases detected. It can be estimated from the PPV. Sensitivity and specificity are characteristics of the test and are only influenced by the test characteristics and the criterion of positivity that is selected. In contrast, the positive predictive value of a test, or the yield, is very dependent on the prevalence of the disease in the population being tested, in this case, on the mortality. The higher mortality is in the population being screened, the higher the positive predictive values (and the yield).

The NECPAL CCOMS-ICO© tool presents high NPV, which is extremely convenient for screening purposes, but low PPV, or yield. Cases detected at 12 and 24 months were lower than 34% and 46%, respectively. The primary means of increasing the yield of a screening program should be to target the tool to groups of people who are at higher risk of death. Identifying individuals at high risk of death is, therefore, required.

Despite the high proportion of false-positives and the low incidence of mortality, the NECPAL CCOMS-ICO© tool presents a sensitivity good enough to correctly discriminate nearly all individuals who will die at 3, 6, 12 and 24 months and a NPV sufficiently high to correctly predict nearly all the individuals who will live. Both predictive values are important for a screening tool intended to identify such a vulnerable and often undetected and under-treated population.

Tests can be used in combination to improve either sensitivity or specificity, but at the cost of the other, depending on how a positive outcome for the combination of tests is defined. This principle was initially used to detect cervical cancer by a Pap smear, which had a high sensitivity but a low specificity. As a result, a Pap smear detected nearly all cervical cancers but a high proportion of false positives. By requiring a sequence of positive Pap smears before taking further diagnostic action, however, it was possible to improve specificity of the smear (that is, reduce the false positives) without compromising the already high sensitivity much.[132] Subsequent work led to an improvement on the approach of repeated smears, and a single cervical smear can be simultaneously tested for the DNA of human papillomavirus, another risk factor for cervical cancer, to improve the specificity of a single screen rather than having to rely on repeat Pap testing.[133]

These strategies, repeated testing and simultaneous testing, may be suggested to improve the specificity of the NECPAL CCOMS-ICO© tool, or the SQ as long as criterion of positivity remains unchanged, as a single screen.

The predictive validity for mortality of the NECPAL CCOMS-ICO© tool per condition and setting of care deserves specific interpretation.

PPV is higher in cancer, followed by dementia and organ failure and, finally, advanced frailty. This finding is unsurprising given the different mortality within these different conditions. It should be emphasized that advanced frailty was assessed by subjective clinical judgment without specific or standardized measures. The diagnostic criteria for advanced frailty are much wider,[134 135 136] which could explain greater variability in identification and low mortality within this condition, especially in primary care centres.

NPV is lower within conditions of cancer and, especially, dementia. This finding is explained by high proportions of false negatives among this groups. Furthermore, non-significantly differences in mortality rates between NECPAL+ and NECPAL- populations (only at 24 months in individuals with cancer) and no difference in risk of death for those with positive and negative identification would suggest that validity of the NECPAL CCOMS-ICO© tool within this conditions would be worse than validity within conditions of organ failure and advanced frailty, probably explained by a sample bias related to a less heterogeneous and a more seriously ill population. Higher incidence of mortality and highest frequencies of disease-specific indicators of severity and progression presented by individuals with these two conditions would support this interpretation. Smaller samples sizes could also be influencing these results.

Despite this variability among conditions, as sensitivity and NPV are high, the NECPAL CCOMS-ICO© tool and the SQ may be used, with a reasonable degree of accuracy, to screen for early palliative care in individuals with cancer,[137 138] dementia, advanced frailty and organ failure[131] as a first test that would be confirmed over time by repeated testing or simultaneous testing.

PPV is higher in intermediate care centre and acute bed hospital, followed by nursing homes. Given that patients admitted to such centresð which focus on palliative care, rehabilitation, and nursing care, often in older patients or those with terminal illnessesð typically suffer from more serious conditions than patients at primary care centres, mortality is expected to be higher. This findings are also unsurprising as PPV depends on mortality, pointing out a better yield of the screening tool in these settings of care compared to primary care centres. Nevertheless, the absolute number of cases detected is higher in primary care centres than in the other settings of care taken as a whole, an important issue from a public health perspective.

Lowest specificity is observed in acute bed hospital. Non-significantly differences in mortality rates between NECPAL+ and NECPAL- populations (only at 24 months) are observed, with the highest proportion of false positives. Nevertheless, sensitivity and NPV are the highest possible. Although the small studied sample could be influencing these results, they highlight the crucial importance of proper management of false positives to accept the suitability of screening.

As sensitivity and NPV are high in all setting of care, the NECPAL CCOMS-ICO© tool and the SQ may be used, with a reasonable degree of accuracy, to screen for early palliative care in primary care centres,[94] intermediate care centres, acute bed hospitals[139] and nursing homes[93] as a first test that would be confirmed over time by repeated testing or simultaneous testing.

Predictive validity of the NECPAL CCOMS-ICO© tool has been evaluated to predict mortality. Nevertheless, a person centred approach based not on diagnosis or prognosis, but on the needs of patients underpins pragmatic approach for identifying individuals who may benefit from an early palliative care intervention. Therefore, predictive validity of available tools to identify these population could also be evaluated to predict unmet palliative care needs.[140] Further research is needed.

Predictive models

The NECPAL CCOMS-ICO© tool has been the first existing available tool to identify individuals with advanced chronic conditions who may benefit from an early palliative care approach that has been employed to develop a predictive model for identifying individuals at high risk of death.

A relatively small number of indicators from the NECPAL CCOMS-ICO© tool, easily obtained from available records or from healthcare professionals, have been proven to be associated with mortality within 24 months. The predictive model developed for identifying ôhigh riskô individuals which relies on these predictors of mortality - identification of palliative care needs by healthcare professionals, infections with systemic impact, the surprise question, severe dependency, individualôs request for palliative care approach, nutritional decline, confusional syndrome, co-morbidity and age- shows excellent discrimination at 3 and 6 months and acceptable discrimination at 12 and 24 months, with good sensitivity and specificity.

The indicators associated with mortality within 24 months among those included in the NECPAL CCOMS-ICO© tool vary according to advanced chronic condition ï cancer, dementia, advanced frailty and organ failure- and according to setting of care ï primary care centres, intermediate care centre, acute bed hospital and nursing homes-. The simple predictive models developed for identifying ôhigh riskô individuals per condition show outstanding and excellent discrimination at 3 months in advanced frailty and organ failure, respectively, and excellent discrimination at 12 months in cancer, with good sensitivity and specificity in all cases. Regarding predictive models developed per setting of care, excellent discrimination is shown at all studied time points in intermediate care centre and acute bed hospital, as well as at 3 and 6 months in primary care centres, all of them with good sensitivity and specificity, although with more complex models.

In light of these results, end of life trajectories might turn out to be an excellent conceptual framework for the development of predictive models.

The identification of palliative care needs by healthcare professionals is the indicator included in the NECPAL CCOMS-ICO© tool which is associated with a higher risk of death, followed by the surprise question, which already showed its predictive validity as screening tool for early palliative care. Although process of judgement and clinicianso estimates have been reported to be biased,[49] these results highlight, however, that the ability of physicians to predict outcome is a valuable and logical standard on which to base the prospective evaluation of a prediction rule[141] [142] and, even more, the advantage to combine the clinicianôs predictions, influenced by unquantifiable random variables which influence the patients survival, as an additional covariate together with objective prognostic factors in a statistical model in order to improve prediction, [143] [144] as has been done in the developed predictive model.

Among the nine indicators included in the NECPAL CCOMS-ICO© tool associated with a higher risk of mortality within 24 months after identification, 4 indicators were of severe advanced frailty -infections with systemic impact, severe dependency, nutritional decline and confusional syndrome-. This results are consistent with available evidence, as solid death predictive variables that have been proven to be reliable indicators of end of life situation.[145] [146] [147] [148] Co-morbidity (Charlson index) and age are also associated with a higher risk of mortality within 24 months.

Frail elderly people have a higher risk of disability compared to non-frail elderly people.[149] [150] [151] Persistent or progressive disability has been associated with a higher risk of dying in older people, especially when functional ability declines rapidly.[152] The risk of disability increases with age and there is a significant association between disability and morbidity and mortality.[153] Although frailty seems to be a distinct geriatric concept, it also overlaps with morbidity and disability.[154] Study results and available evidence would support

recommendation that severe advanced frailty and, thus, substantial disability should be considered for palliative care for control of symptoms, care planning, and increased support with personal care needs.[155]

Individualôs request for palliative care approach is also predictive of death, highlighting the extremely valuable information that individuals do provide and strengthening underlying reasons for a person centred approach to make clinical decisions predicated on the attainment of individualsô goals of care.[112]

These findings guarantee the content validation of the NECPAL CCOMS-ICO© tool which, compared with similar existing tools,[90 21 91 93 94 95] is strengthened by containing indicators of severe advanced frailty, disability and request of the patient for palliative approach as a triggers to identify individuals likely in need of palliative care and as reliable indicators of end of life situation, the value of which has been proven.

When modelling a Cox proportional hazard model, a key assumption is proportional hazards, that is to say, hazard ratios are constant over time. Evaluation of the proportional hazards assumption is essential since its violation raises questions regarding the validity of Cox model results which, if unrecognized, could result in the publication of erroneous scientific findings.[156]

In this study, the hazard ratio, that is to say, the relative risk of death within 24 months in individuals presenting versus not presenting some of the identified predictive indicators, is constant over time for all of them except for two predictors -ñidentification of palliative care needs by healthcare professionalsò and ñnutritional declineò-, that have been shown to predict mortality only within 6 months. After this time point they do not predict mortality in the population-based studied sample.

There are various opinions on the importance of the proportional hazards assumption with regard to the parameters interpretation. Some authors state that

violation from it is nothing extremely problematic as, in such cases, parameter for a covariate for which assumption is not satisfied can be understood as óaverage effectô over time points that are observed in a dataset.[157] The others, however, underline the importance of this assumption and suggest potential modification of the model if hazard ratio turns out not to be constant over time for some covariates.[158] In such cases, it would be worth taking this fact into account and estimate the model adjusting for potentially time varying effect of covariate for which assumption is not satisfied rather than stating that parameter estimate for this covariate expresses its óaverage effectô on the hazard level.

It is hard to define a general rule for non-proportional hazards handling, as one of the three available possibilities (i.e. keeping all covariates in the model and neglecting the fact of the violation from non-proportional hazard assumption, introducing interaction with time and estimation of stratification model) can be taken into consideration. It is also hard to compare these models, especially stratification model with non-stratified models, as they differ in their construction. The latter approach enables to obtain parameter estimate for covariate for which proportional hazard assumption is violated, as well as analyse how hazard ratio changes over time, which is impossible if stratification model is chosen. The choice of the method needs to be adjusted for the particular situation.[159]

To handle non-proportional hazards in this study, the three available possibilities have been considered. Modelôs discrimination ability has been estimated keeping all covariates in the model and neglecting the fact of the violation from non-proportional hazard assumption, assuming the expression of óaverage effectô on the hazard level for ñidentification of palliative care needs by healthcare professionalsò and ñnutritional declineò. However, introducing interaction with time and estimation of stratification model have also been considered, providing helpful inputs to understand the underlying explanation of behaviour of these death predictive indicators. The variation of their effect through time was probably related to heterogeneity of studied sample, as stratification model importantly pointed it out.

The development of predictive models for identifying individuals at high risk of death per condition, that is to say, per end of life trajectory,[34 35 36 37] allowed to split the whole sample into potentially more homogeneous subgroups which revealed, on one hand, the identification of different indicators associated with mortality within 24 months according to end of life trajectory and, on the other hand, the development of more simple predictive models with proportional hazards for all identified predictive indicators.

In dementia, although identification of palliative care needs by healthcare professionals and pressure sores GIII-IV have been identified as predictors of mortality within 24 months, any good predictive model could be developed. Almost 90% of recruited patients presented disease-specific indicators of severity and progression, becoming the most seriously ill group recruited.

When distribution of disability trajectories in the last year of life has been evaluated according to the conditions leading to death, a predominant trajectory of persistently severe disability has been reported only for subjects who die from advanced dementia.[37] Thus, this probable sample bias, which reflects the pattern of persistent severe disability typical of advanced dementia, and which has been identified as predictor of mortality,[160] could explain the impossibility of developing a predictive model which would be able to discriminate between individuals with a risk to die or to be alive essentially because it is based on indicators related to severe advanced frailty and disability, already present in almost all recruited individuals. In light of these results, the predictable pattern of persistent severe disability typical of advanced dementia should also be considered for palliative care for control of symptoms, care planning, and increased support with personal care needs.[155]

In cancer, and despite a probable sample bias -recruited population not much heterogeneous and seriously ill -, some indicators associated with mortality within 24 months among those included in the NECPAL CCOMS-ICO© tool have been identified -identification of palliative care needs by healthcare professionals,

carerôs request for palliative care approach and severe emotional distress-. These findings would strengthen evidence regarding patient related factors, such as performance status, symptoms and laboratory parameters, as more predictive of imminent death from cancer than are tumour related factors such as grade, stage, or genetic signatures.[161] The absence of indicators related to severe advanced frailty among those identified as predictors of mortality could be explained by the pattern of decline at the end of life typical of cancer, with disability and functional decline appearing quite late in the course of the illness[34 35 36] and, thus, still not present when individuals were recruited or by a probable sample bias with a recruited population already presenting frailty.[37] Further research is needed.

Individuals who were identified as in need of palliative care by healthcare professionals had more than 3 times the risk of death compared to individuals not identified. This relevant hazard ratio and the fact that the highest modelôs discrimination -excellent- is observed at 12 months, exactly the time point explored by the surprise question, would evidence the more predictable nature of monophasic and easier to anticipate pattern of decline typical of cancer.[43 44]

Additional indicators included in the developed predictive model for cancer were carerôs request for palliative care approach and severe emotional distress. The NECPAL CCOMS-ICO© tool is the only such tool, compared with similar existing ones,[90 21 91 93 94 95] which integrated emotional distress and the request of the carer for palliative approach as a triggers to identify individuals likely in need of palliative care. These findings strengthen, again, its content validity.

Advanced frailty is the most common condition among recruited population, mainly recruited in primary care services. It has been assessed by subjective clinical judgment without specific or standardized measures, which has probably lead in greater variability in recruitment and, consequently, in a more heterogeneous group.

Except identification of palliative care needs by healthcare professionals, all indicators associated with mortality within 24 months in this condition are, as could be expected, deficits caused by severe advanced frailty, specifically with geriatric syndromes -infections with systemic impact, confusional syndrome and falls- and use of resources -complex/intense nursing care needs and urgent admissions-. Co-morbidity (Charlson index) and age are also associated with a higher risk of mortality. Heterogeneous sample and appropriate indicators,[145 148 162 163 152 153 154] would explain the development of an outstanding predictive model at 3 months, as well as acceptable predictive models at 6, 12 and 24 months.

Frequent emergency department users appear to experience higher mortality and hospital admissions compared with non-frequent users.[163] Disability is an adverse outcome of frailty that places a high burden on frail individuals, care professionals and health care systems.[164] Most decedents have high levels of disability in the last month of life, yet more than half are not disabled 12 months before death. Around 60% of subjects who die from frailty present progressive, catastrophic or accelerated disability in the last year of life (only 25% present severe disability during the entire year) suggesting that frailty, and subsequently disability, mainly appear and worsen during this period of time.[37] This evidence is consistent with study findings and the possibility of a predictable death in the end of life trajectory of frailty.

Although frailty and dementia share illness trajectory of functional decline at the end of life,[34 35 36] according to available evidence regarding severe advanced frailty indicators and pattern of disability 12 months before death, and even predictive validity for mortality of the NECPAL CCOMS-ICO© tool in these conditions, it would be justified to consider frailty and dementia as two different groups for analysis and two different end of life trajectories, as has been done throughout studies I, II and III.

Organ failure is the second most common condition among recruited population, and has been mainly recruited in primary care centres. Disease-specific indicators

of severity and progression have not been analysed to identify indicators associated with mortality within 24 months on account of small samples of individuals in some diseases but also assuming that older adults are more likely to have more than one chronic disease.[14 59]

Regarding indicators associated with mortality within 24 months, geriatrics syndromes predicting death are exactly the same as in advanced frailty -infections with systemic impact, falls and confusional syndrome- and, additionally, severe dependency. Complex/intense nursing care needs and age, are also associated with a higher risk of mortality, as in advanced frailty. The only two indicators that are death predictors in advanced frailty and are not in organ failure are co-morbidity (Charlson index) and urgent admissions, a relevant fact which would suggest that both co-morbidity and, especially, urgent admissions are equally frequents among individuals who will die or will be alive.

Carerôs request for palliative care approach, as shown in cancer, is a death predictor in organ failure. This result importantly point out the relevance and valuable information that carers can provide regarding prognosis in severely affected individuals with these long illness trajectories.

Organ failure is the only condition where the surprise question is a predictor of mortality within 24 months. In fact, it is the best death predictor within this condition. The availability of information provided by disease-specific indicators of severity and progression, probably contributing to improve estimations and clinical judgement, could explain this result. Nevertheless, organ failure is the only end of life trajectory where the identification of palliative care needs by healthcare professionals is not a predictor of mortality, demonstrating the lack of palliative assessment and integration of palliative care into medical specialties.[165 166 167]

It is remarkable, however, that 8 predictive indicators,[145 162 148 146 153] easily obtained from available records or from healthcare professionals, have made

possible the development of an excellent predictive model at 3 months, as well as acceptable predictive models at 6, 12 and 24 months.
Unfortunately, the evaluation of the proportional hazards assumption in predictive models developed per setting of care, although presenting excellent discrimination at all time point studied in intermediate care centre and acute bed hospital, as well as at 3 and 6 months in primary care centres, identifies some indicators for which the effect is non proportional, meaning that they are time dependent covariates. The variation of their effect through time is again, probably, related to heterogeneity of studied sample in each setting of care, as seen with general predictive model.

Only in nursing homes, the hazard ratios for all indicators in the developed predictive model are constant over time. Nevertheless, poor modelôs discrimination between individuals with a risk to die or to be alive could be explained by main condition suffered by residents in nursing homes, that is, dementia, for which any good predictive model could be developed.

As none of available possibilities to handle non-proportional hazards has resulted satisfactory or better than to split the whole sample into more homogeneous groups to develop predictive models per end of life trajectory, no further analysis have been considered in settings of care, taking into account small sample sizes in intermediate care centre and acute bed hospital. More research, with sample sizes large enough to allow the development of predictive models per end of life trajectory in each setting of care would be needed.

Strengths and limitations

The strengths of these studies include the field-assessments on large samples of individuals prospectively assessed and identified in different settings of care

(community, hospitals and residential homes) to be sure to collect all possible cases of patients likely in need of palliative care.

The recruitment was carried out with 100% of participation from both healthcare professionals and settings of care that needed to be involved, a common case identification methodology followed in all settings and a high level of commitment from all participants.

The studies have some limitations. Due to non-probabilistic sampling applied, it is not possible to determine representativeness of the study population-based sample. Recruitment was conducted in a relatively small district that may not be truly representative of the region as a whole. However, the primary care centres were randomly selected, and represent 32.9% of the entire Countyôs population.

Recruitment may have also been affected by ageing population and strong influence of geriatric care in the area, as well as by length of the study window.

Availability of quantitative data in clinical charts may have affected description of patientsôcharacteristics and predictive indicators identified.

Another potential limitation is the risk of selection bias, as inclusion criteria were based on clinical judgment, which is inherently subjective and can vary depending on the setting of care or the healthcare professional. To minimize this bias, all definitions, procedures, and measures were standardised and adhered to in accordance with the study operations manual.

As this study was based on health professionalsô assessment and routine data, patientsôperspective was not included.

For certain conditions and settings of care, a relatively limited number of patients were evaluated, thus potentially limiting the validity and generalizability of some results.

Some predictive models seem to have some ability in identifying the population of interest, indicating good internal validity. These results are optimistic by definition as they derive from the best model that fits the data. The external validity is unknown and, thus, the predictive ability of these models should be validated in another sample.

X. Conclusions

Study I

The most relevant contribution of this study to the body of knowledge of palliative care consist in the innovative assessment of the population-based needs for palliative care through identifying prospectively the population-based prevalence of individuals with advanced chronic conditions who may benefit from an early palliative care approach using the NECPAL CCOMS-ICO© tool.

Methodologies based on retrospective assessments from causes of death, can also provide valid estimates. Nevertheless, they are not useful for improving clinical practice, as they do not allow to identify patients in clinical settings, while this innovative approach is potentially transferable to the clinical practice and allows prospective identification.

There is a clear dissonance between the focus on cancer of most specialist palliative care resources and the prevalence of individuals who may benefit from an early palliative care approach. A significant shift in thinking is required on how health systems identify and manage individuals with advanced chronic conditions, mainly community-dwelling and nursing-based people suffering from advanced frailty, organ failure and dementia.

General clinical indicators of severity and progression are present in almost all identified individuals who may benefit from an early palliative care approach, regardless of suffered advanced chronic condition, highlighting the importance of these kind of indicators and of such innovative approach, based on the accumulation of deficits to define severe advanced frailty, to identify this population.

Scant performance differences exist between SQ+ identification and NECPAL+ identification, as currently defined, (SQ+ and, at least, one positive additional

indicator). Consequently, both tools, NECPAL CCOMS-ICO© and SQ, may be equally employed to identify individuals with advanced chronic conditions who may benefit from an early palliative care approach, although the NECPAL CCOMS-ICO© tool allows the completion of systematic multi-dimensional assessments, which makes it more recommendable than using the SQ exclusively.

The consistent and systematic use of the NECPAL CCOMS-ICO© tool across all participating clinical settings shows that identification of individuals with advanced chronic conditions who may benefit from an early palliative care approach is feasible and can be performed in any setting of care in daily clinical practice via multi-disciplinary assessment.

Study II

The NECPAL CCOMS-ICO© tool may be used, with a reasonable degree of accuracy, to screen individuals for early palliative care. It presents high sensitivity and high NPV, an important finding given the consequences of failing to identify this vulnerable and often undetected and under-treated population.

Scant differences in predictive validity for mortality exist between SQ+ identification and NECPAL+ identification, as currently defined, (SQ+ and, at least, one positive additional indicator). Consequently, both tools, NECPAL CCOMS-ICO© and SQ, may be equally employed to screen individuals for early palliative care.

There is an overestimation of mortality and, accordingly, a high proportion of false positives identified, individuals who test positive even though they really will not die. As some of the individuals identified will end up living for years in a fragile state, although some others will die soon, all typically need the services that are priorities in the last part of life: advance care planning, comfort measures,

assistance for daily activities, family support, and so forth. This required arrangement of care and services is of crucial importance to accept the suitability of screening.

The NECPAL CCOMS-ICO© tool and the SQ provide early identification of individuals that present a higher risk of death, thus enabling early assessment and delivery of early palliative care in individuals who screen positive and, effectively, present unmet palliative care needs. Further additional assessments are, then, recommended.

The predictive validity for mortality of the NECPAL CCOMS-ICO© tool and the SQ per condition and setting of care show PPV, and yield, according to expected mortality. Per condition, higher in cancer and dementia, followed by organ failure and, finally, advanced frailty, but with quite similar absolute number of cases detected in each group; per setting of care, higher in intermediate care centre, acute bed hospital and nursing homes and, finally, primary care centres, but with absolute number of cases detected in primary care centres higher than in the other settings of care taken as a whole. This is an important issue from a public health perspective, making advisable to screen individuals for early palliative care regardless of advanced chronic condition and in all settings of care.

Sensitivity and NPV are acceptably high in all conditions and settings of care, which would justify to screen individuals for early palliative care using the NECPAL CCOMS-ICO© tool and the SQ as a first assessment, accompanied by additional tests.

Study III

A relatively small number of indicators from the NECPAL CCOMS-ICO© tool, easily obtained from available records or from healthcare professionals, have been proven to be associated with mortality within 24 months and useful to develop simple predictive models for identifying individuals at high risk of death.

The NECPAL CCOMS-ICO© tool is essentially based on indicators related to severe advanced frailty and disability, and strengthened by containing psychological domain as well as request of individual and family for palliative approach as a triggers to identify individuals in need of palliative care. All of them have been proven to be predictors of mortality and useful to develop simple predictive models, which would prove its content validity.

The indicators associated with mortality within 24 months among those included in the NECPAL CCOMS-ICO© tool vary according to advanced chronic condition and according to setting of care, making clear the heterogeneity of the study population-based sample, heterogeneity equally seen among settings of care, and explaining the difficulties to develop simple predictive models.

End of life trajectories, a criterion to split the study population-based sample into potentially more homogeneous subgroups, may turn out to be an excellent conceptual framework for the development of simple predictive models, particularly in advanced frailty and organ failure, the most prevalent population-based advanced chronic conditions, where indicators of severe advanced frailty, and subsequently disability, mainly appear and worsen throughout 12 months before death. The simple and promising predictive models that have been developed should be externally validated.

The indicators included in the NECPAL CCOMS-ICO© tool that have been proven to be associated with mortality within 24 months could be useful to review the current criterion of positivity of the tool which could lead, potentially, to a better identification of ôhigh riskô individuals and, consequently, to an improvement of specificity and PPV, and yield. This potential improvement of the predictive validity for mortality of the NECPAL CCOMS-ICO© tool to be employed as screening tool for early palliative care should be tested.

Overall conclusion

The NECPAL CCOMS-ICO© tool can be considered useful in identifying individuals with advanced chronic conditions who may benefit from an early palliative care approach.

It can be employed to assess the population-based needs for palliative care through identifying prospectively the population-based prevalence of this population, an innovative approach which can be potentially useful for improving clinical practice.

It can be used, as well as the SQ, as screening tools for early palliative care. It can be employed as a first assessment to identify this population, preferably accompanied by repeated or additional tests, aiming to improve specificity.

Finally, some of the indicators included in the NECPAL CCOMS-ICO© tool have been proven to be associated with mortality within 24 months, which would prove its content validity. From a population-based perspective, end of life trajectories may turn out to be an excellent conceptual framework for the development of simple predictive models for identifying individuals at high risk of death, particularly in advanced frailty and organ failure, the most prevalent population-based advanced chronic conditions, for which simple and promising predictive models have been developed and should be externally validated.

XI. Considerations for further research

Population-based prevalence needs to be confirmed by similar studies in different and equivalent demographic areas and settings of care.

Construct validity of NECPAL CCOMS-ICO© tool has been just partially explored. Additional analysis, such as internal consistency and reliability remain unexplored.

Evidence is needed regarding the expected improvement of the predictive validity for mortality of the NECPAL CCOMS-ICO© tool, specifically specificity and PPV, whether criterion of positivity is reviewed according to predictors of mortality per end of life trajectories.

In the same way, evidence is needed regarding the expected improvement of the predictive validity for mortality of the NECPAL CCOMS-ICO© tool, specifically specificity and PPV, whether repeated testing and simultaneous testing are implemented.

Predictive validity of the NECPAL CCOMS-ICO© tool has been evaluated to predict mortality. Nevertheless, it could also be evaluated to predict unmet palliative care needs.

Trials need to be conducted to determine whether the effect of implementing screening for early palliative care using the NECPAL CCOMS-ICO© tool lead to earlier palliative care intervention and this, in turn, lead to better outcomes.

More research, with sample sizes large enough to allow the development of predictive models per end of life trajectory in each setting of care are needed.

Developed simple predictive models per end of life trajectory need to be externally validated and large prospective trials need to be conducted to prove the predictive modelsô ability to identify individuals who are at high risk of death to better target early palliative care interventions to reduce suffering and improve quality of life.

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