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Relevance of Comorbidity Indices in Chronic Kidney Disease

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Relevance of Comorbidity Indices in Chronic Kidney Disease

Dissertação de candidatura ao grau de Mestre em Medicina, submetida ao Instituto de Ciências Biomédicas Abel Salazar – Universidade do Porto

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CHAVE MÓVEL

Ao meu filho Vicente,

“somos do tamanho dos nossos sonhos”

Fernando Pessoa

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RESUMO

A doença renal crónica é atualmente um sério problema de saúde a nível mundial que está associado a um aumento da morbilidade e mortalidade. A maioria dos doentes com doença renal crónica são adultos idosos, com um certo grau de fragilidade e impacto funcional, que possuem também outras comorbilidades, tais como, a hipertensão e a diabetes. A multimorbilidade e polifarmácia presente nestes doentes leva a um aumento do risco de desfechos clínicos adversos, tais como redução da qualidade de vida, hospitalizações frequentes, readmissões hospitalares, declínio funcional e mortalidade.

Uma vez que esta população e doentes é grande utilizadora dos serviços de saúde, a estratificação de risco destes doentes é de grande importância e pode ajudar os clínicos a planear uma alocação de recursos adequada e custo efetiva, de acordo com as necessidades individuais.

Adicionalmente, numa era da prática clínica "costumizada", adaptada às necessidades e preferências dos doentes, os scores de estratificação e risco são de extrema importância no auxílio dos clínicos para tomada de decisão terapêutica partilhada.

O objetivo desta revisão bibliográfica é realçar a relevância da avaliação da multimorbilidade nos doentes renais crónicos, bem como, analisar a utilidade e aplicabilidade dos índices de medição de comorbilidade, como ferramentas de estratificação de risco, para a população de doentes com doença renal crónica. A base de dados Medline (via pubmed) foi utilizada para pesquisa de artigos em língua inglesa publicados nos últimos 10 anos. Foram utilizadas na pesquisa as seguintes palavras-chave: "Chronic Kidney Disease, Multimorbidity, Comorbidity Indices, Risk Stratification, Charlson Comorbidity Index, Elixhauser's Comorbidity Index, Chronic Disease Score, Multidimensional Prognostic Index e Comprehensive Geriatric Assessment".

À luz da mais recente evidência, os *scores* de comorbilidade, tais como o Índice de Comorbilidade de Charlson, podem ser de grande utilidade para o uso clínico diário, de modo a prever desfechos clínicos adversos e a mortalidade, facilitando a alocação de recursos e a tomada de decisão terapêutica. Outros instrumentos multidimensionais de estratificação de risco são desejáveis, contudo a sua complexidade e os recursos técnicos envolvidos ameaçam o seu uso na unidades clínicas.

Palavras-chave: Doença Renal Crónica, Multimorbilidade, Índices de Comorbilidade Estratificação de Risco

ABSTRACT

Chronic kidney disease is now a serious global health problem associated with increasing morbidity and mortality. The majority of patients with chronic kidney disease are old and frail adults with other co-existing health conditions such as hypertension and diabetes. The multimorbidity and polypharmacy present in these patients increase their risk of poor clinical outcomes such as reduced quality of life, frequent hospitalization, readmission, functional decline, and mortality. Due to the massive usage of healthcare systems by this frail population, patient's risk stratification tools can help clinicians planning an adequate and cost-effective resources allocation, according to the individual needs. Moreover, in the era of a customized clinical practice, tailored to patients' preferences and needs, risk stratification scores are extremely important to help clinicians in a shared treatment decision-making.

The objective of this bibliographic review is to highlight the relevance of multimorbidity evaluation in chronic kidney disease patients, as well as, to analyze the utility and applicability of comorbidity measurement indices, as risk stratification tools, for chronic kidney disease patients' population. The Medline database (via pubmed) was used to search for English-language articles published in the last 10 years. The keywords used in this search were, Chronic Kidney Disease, Multimorbidity, Comorbidity Indices, Risk Stratification, Charlson Comorbidity Index, Elixhauser's Comorbidity Index, Chronic Disease Score, Multidimensional Prognostic Index and Comprehensive Geriatric Assessment. From different keyword combinations, in total 146 articles were used for this review.

In the light of the latest evidence, comorbidity scores such as Charlson Comorbidty Index can be of great utility in a bedside and daily usage, to predict renal patients' poor outcomes and mortality, allowing a convenient resources allocation and facilitating decision-making process.

Other multidimensional risk stratification instruments are desirable, but the complexity and involved technique resources threaten their use in clinical units.

Keywords: Chronic Kidney Disease, Multimorbidity, Comorbidity indices, Risk stratification

ABBREVIATIONS

CKD – Chronic Kidney Disease

TNF – Tabela Nacional de Funcionalidade

ICF - International Classification of Functioning, Disability and Health

ESRD – End-Stage Renal Disease

eGFR – estimated Glomerular Filtration Rate

RRT – Renal Replacement Therapy

RFD - Renal Function Decline

PD – Peritoneal Dialysis

ASA - American Society of Anesthesiologists

MELD - Model for End-stage Liver Disease

INR - International Normalized Ratio

CCI - Charlson Comorbidity Index

ACCI - age-adjusted Charlson Comorbidity Index

mCCI-IHD - modified CCI in Incident Hemodialysis Patients

MINS - Myocardial Injury after Non-cardiac Surgery

ICD - Implantable Cardioverter-Defibrillator (ICD)

CMML - Chronic Myelomonocytic Leukemia

ECI - Elixhauser’s Comorbidity Index

CDS - Chronic Disease Score

M-CDS - Modified-Chronic Disease Score

WHO – World Health Organization

CGA - Comprehensive Geriatric assessment

MPI - Multidimensional Prognostic index

METHODS

In the present bibliographic review, it was used for literature search the Medline database (via pubmed) to search for English-language articles published in the last 10 years. Exceptionally, few articles published before were also included due to their relevance to this subject. The keywords used in this search were, Chronic Kidney Disease, Multimorbidity, Comorbidity Indices, Risk Stratification, Charlson Comorbidity Index, Elixhauser's Comorbidity Index, Chronic Disease Score, Multidimensional Prognostic Index and Comprehensive Geriatric Assessment. From different keyword combinations, in total 146 articles were used for this review.

1 MULTIMORBIDITY

Throughout the ages, the humanity observed an increase in longevity as consequence of all the efforts made, to improve health care systems, health education and promotion, public health measures, economic and social development of populations and the significant scientific advance[1]. Despite being a great achievement, an increased longevity inevitably leads to the development and accumulation of chronic diseases in humans[2]. Multimorbidity is defined as the presence of two or more long-term diseases including physical and mental health conditions, ongoing conditions such as learning disability, symptom complexes such as frailty or chronic pain, sensory impairment such as sight or hearing loss or even alcohol and substance misuse[3]. A systematic review and meta-analysis of 70 studies, revealed that, a large proportion of the global population, especially those above the age of 65, are affected by multiple chronic diseases[4]. Multimorbidity is prevalent in 50-60% of adults aged 65 years or older[4]. However, multimorbidity is not only a consequence of getting older as it can also occur in children or younger adults[5] as well as younger people living in deprived areas[6].

The clinical relevance of having multiple long-term conditions is its association with poor health outcomes, such as, reduced quality of life, frequent hospitalization, readmission, functional decline and mortality[7–9].

These patients are great healthcare users, with complex medical needs, overlapping physical and mental health disorders, frailty and polypharmacy[10]. Multimorbidity is also inevitably related to increased healthcare costs[11].

1.1 MULTIMORBIDITY IN CHRONIC KIDNEY DISEASE

Chronic kidney disease (CKD) affects approximately 10% of adult population worldwide. According to the 2017 Global Burden of disease study, CKD resulted in 1.2 million deaths and was the 12th leading cause of death worldwide[12].

CKD is related with a high levels of patient mortality and morbidity and frequently affects people with other co-existing health conditions [13,14]. The presence of comorbidities in these patients is higher (approximately 98%) and is associated with adverse clinical outcomes such as mortality, hospitalization and length of stay[15,16].

The health complications that come with CKD affect all body systems causing a reduction of quality of life compared with health people[17].

The comorbidities that share the pathophysiology and/or pharmacological treatment with CKD are called concordant comorbidities (Hypertension, Peripheral Vascular Disease, Heart

Failure, Stroke and Transient Ischaemic Attack, Atrial Fibrillation, Diabetes and Coronary Heart Disease). Diabetes and hypertension besides being examples of concordant comorbidities, are also the main causes of CKD[16].

The comorbidities which the pathophysiology is unrelated and/or treatments are complicating, or contradictory are called non-concordant comorbidities (Rheumatological Conditions, Chronic Obstructive Pulmonary Disease, Inflammatory Bowel Disease, Parkinson Disease, Multiple Sclerosis, Glaucoma, Chronic Liver Disease, Prostate Disorders, Thyroid Disorders). Mental disorders such as Depression, Anxiety and Dementia are also common in these patients.[16] Obesity was also described as a very frequent comorbidity in CKD patients[18].

2 FRAILTY

Frailty is defined as a state of increased vulnerability resulting from aging-associated decline in reserve and function across multiple physiologic systems such that the ability to cope with every day or acute stressors is comprised[19].

Frailty is frequent in elderly and entails a higher risk for poor health outcomes including falls, incident disability, hospitalization, and mortality[20].

Fried et al. has defined frailty as meeting three out of five phenotypic criteria indicating compromised energetics: low grip strength, low energy, slowed waking speed, low physical activity, and/or unintentional weight loss[21]. The subset of patients presenting only one or two criteria are in a pre-fail-stage and are at higher risk of progressing to frailty[21].

Frailty overlaps multimorbidity due to the widespread health deficit accumulation that leads in some cases to functional impairment and higher risk of adverse outcomes such as falls, disability, nursing home admission, hospitalization, and mortality[22]. Therefore, frailty can be used as a method of identifying older people with multimorbidity who are particularly vulnerable to a wide range of adverse outcomes, with individual and social relevance [22].

Despite most older people with frailty have multimorbidity, the majority of people with multimorbidity are not frail[21].

Frailty can be assessed in primary care and community care by an informal assessment of gait speed (for example, time taken to walk from the waiting room, in which more than 5 seconds to walk 4 meters indicates frailty), self-reported health status ("how would you rate your health status on a scale from 0 to 10", with scores of 6 or less indicating frailty) and PRISMA-7 questionnaire, with scores of 3 and above indicating frailty[23]. In hospital outpatient frailty can be assessed, using the same tools as for primary care plus the "Time Up and Go" test (with times of more than 12 seconds indicating frailty) and the self-reported physical activity, with frailty indicated by scores of 56 or less for men and 59 or less for women using the Physical Activity Scale for the Elderly[23]. The only particularity is that a physical performance tool cannot be used to assess frailty in a person that is acutely unwell [23].

2.1 Frailty evaluation in Chronic Kidney Disease

Frailty is highly prevalent in CKD, with prevalence increasing with worsening kidney function, being highest in patients receiving dialysis[25]. Two-thirds of dialysis-dependent CKD patients were classified as frail[26]. Moreover, frail patients with CKD have worse outcomes than those who are robust with CKD, including increased falls, hospitalization and mortality rate[27,28].

The pathophysiology behind CKD-associated frailty is not completely understood. Jeffery et al., shown that in many chronic diseases, frailty is associated with inflammation[20] and other previous study show that pro-inflammatory cytokines such as IL-6 and TNF-α, may play a role in age-related muscle atrophy and sarcopenia typically seen in frailty[29]. Similarly, it was described that in patients with renal insufficiency, the levels of pro-inflammatory cytokines are also raised[30].

Once frailty can be used to predict poor outcomes in patients with CKD, such as increased risk of hospitalization and mortality, it is imperative to address which methods of frailty assessment can be used in CKD, in order to identify those who may benefit from targeted intervention[25].

There are several concepts of frailty, which differ in the degree of physical, psychological and social components. The Fried Frailty Phenotype and the Frailty Index are the two most popular concepts of frailty[31,32]. Although, the Frailty Phenotype gathers more robust evidence in terms of predicting outcomes in CKD patients, it becomes a time-consuming method involving a combination of questionnaires and physical assessments, being not practical for a routine use within nephrology outpatients' services[33].

Nixon et al., evaluated the diagnostic accuracy of several frailty screening methods in patients with CKD G4-5 and those established on hemodialysis (G5D), using the Frailty Phenotype as the reference standard[33]. In this study, the Clinical Frailty Scale, PRISMA-7, CKD Frailty Index, CKD FILAB, walking speed, hand grip strength and Short Physical Performance Battery were evaluated. Overall, the walking speed was the most discriminative measure and can be used to accurately screen for frailty in patients with advanced CKD. As alternative, in the impossibility to realize a physical assessment to screen for frailty, the Clinical Frailty Scale was the most accurate non-physical assessment frailty screening methods, and currently has the strongest evidence base for prognostication in advanced CKD populations[33–35].

It is relevant to note that in this study there was a similar age between the non-frail and frail groups highlighting that frailty is a syndrome that is not only due to the aging process and both groups had no statistically significant difference in the Charlson Comorbidity index score showing that comorbidity, though a risk factor, not always overlaps frailty[33].

3 The Impact of Multimorbidity on Healthcare Systems

Aging people with multiple comorbidities tend to be massive users of the healthcare systems, however, to guarantee a high-quality healthcare, resources should be allocated according to the needs of the population instead of the demand[36].

The prediction of healthcare utilization as well as the health outcomes, helps in the decision of resources allocation according to the individual care needs[36]. Risk stratification tools, can be useful, allowing tailored proactive clinical care, installation of preventive measures, healthcare restructuration, and improvement clinicians' insight[36]. The usage of comorbidity measurement tools as a risk stratification tool will allow the improvement of the quality-of-care services as well as costs reduction[36].

The monitorization and prediction of costly patient outcomes such as hospitalization, emergency department visits, or simply patient-specific management requirements such as multidisciplinary care, continued or palliative care can be achieved by the implementation of structured population health management programs[36]. These programs use routinely collected healthcare data to perform stratification analysis in which it stratifies individuals within a specific subpopulation according to the risk of experiencing a poor health outcome or the extent of their healthcare utilization[36]. Due to accessibility, the information collected from hospital data can be used in risk stratification tools[36].

Specifically in nephrology field, Sy and co-authors assessed the costs of frail patients on hemodialysis, followed up for 3 years, and conclude that frail patients incurred 22% higher costs compared with their nonfrail counterparts[37]. Given the massive impact of dialysis's patients on healthcare systems, slight decreases in utilization may lead to cost savings. Sy and collaborators suggest that maintaining patients or returning them to a nonfrail state could save money and decrease mortality[37]. Quality parameters of care must be adjusted to comorbidity and frailty indices in the treated populations.

Identifying comorbid and frail patients through risk stratification tools as well as preventing frailty or improving health of frail dialysis patients, will save money by decreasing the rates of hospitalization, reducing costs of caregivers and costs related to the inability to work[37].

4 PATIENT'S RISK STRATIFICATION – ON THE WAY OF A CUSTOMIZE MEDICAL APPROACH

Due to the global and public health burden inherent to CKD, great efforts have been made to predict and stratify patients' risk of developing unfavorable outcomes, in order to have an effective allocation of resources and to provide the patient with the best possible treatment[38].

In the past, clinicians have mainly used the medical knowledge, their personal experience, and their own "intuition" to make decisions about individual patients. On the other hand, precision nephrology is a branch of medicine that aims to provide information and methodological tools that allow redefinition of CKD in terms of pathogenesis, prevention, prognosis, and treatment besides and beyond clinical intuition[38]. Precision nephrology includes better phenotyping, better insight of disease mechanisms, customization of medical decisions and better risk stratification[38].

To customize the medical approach, NICE guidelines NG56 were created to improve quality of life by promoting shared decisions based on what is important to each person in terms of treatments, health priorities, lifestyle and goals[23].

Once the increase of severity and complexity of conditions, implies an increasing complexity of care services, and results in a growing need for a tailored approach with reduced treatment burden[22], NICE guidelines NG56 sets out which people are most likely to benefit from an approach to care that takes account of multimorbidity, how they can be identified and what the care involves[22,23].

An approach to care that takes account of multimorbidity involves personalized assessment and the development of an individualized management plan, aiming to improve life quality by reducing treatment burning, adverse events and unplanned and uncoordinated care. The approach takes account of person's individual needs, preferences and treatments, health priorities and lifestyle. It aims to improve coordination of care across services, particularly if this has become fragmented[23].

NG56 defined target groups who may benefit from approach to care that takes account of their multimorbidity[23].

- The ones that find it difficult to manage their treatments or day-to-day activities;

- The ones that receive care and support from multiple services and need additional services;
- The ones that have both physical and mental health conditions;
- The ones that have frailty or falls;
- The ones that frequently seek unplanned or emergency care;
- The ones that are prescribed multiple regular medicines.

According to NICE guidelines NG56 People who may benefit from an approach to care that takes account of multimorbidity can be identified opportunistically during routine care or proactively using electronic health records[23].

Figure 1 makes an illustrative representation of multimorbidity in CKD patients' population and all its inherent aspects (Figure 1*, appendix*).

5 Dialysis Doesn't Fit All – The Importance of Multimorbidity clinical assessment in the Treatment Decision-Making Process

End-stage renal disease (ESRD) patients' population includes two groups of patients, the ones who are fit, without severe comorbidity for whom dialysis works as a bridge to transplantation or a long-term maintenance treatment, and the ones that are older, frail, with severe comorbidity, with a limited life expectancy, for whom dialysis is the end-line treatment[39].

Older adults with advanced CKD (eGFR < 30 ml/min/1.73 m^2) often suffer from other significant comorbidities and therefore may die from another cause that is associated with other comorbidities before reach ESRD and require dialysis[40]. Therefore, it is extremely difficult to predict the prognosis and decide which patients benefit from renal replacement therapy (RRT) or conservative care[41].

Rosansky et al., assumed that a patient's pattern of renal function loss over time in relation to their underlying comorbidities can serve as a guide to forecast a future dialysis requirement. Evidence suggest that dialysis does not provide a survival benefit for older adults with poor mobility and high levels of comorbidity[40].

In USA, the one year mortality after dialysis initiation can be 41% from patients aged more than 75 years old, comparing to 28% for patients aged 65-74 and 17% for those aged 45-64[39].

After dialysis initiation, besides decrease in years of life, many older patients experience functional decline and more episodes of hospitalization[42].

Actually, the early start of dialysis does not seem to be of great benefit. A study performed by Rosansky and collaborators, corroborated the guidelines, which recommend deferring dialysis until patients reach levels of eGFR $\leq$ 6 ml/min/1.73 m^2 unless a patient manifest symptom at a higher eGFR level[43].

Although patient's symptoms should be the main determinant for dialysis initiation, many nephrologists still only take into account eGFR levels and the majority of those who start dialysis at an outpatient setting or at the hospital in a context of an episode of acute renal failure, appear to be starting dialysis for a non-specific, non-life threatening symptoms[40].

In agreement to NICE guidelines NG56 about "multimorbidity: clinical assessment and management" to optimize the care of this comorbid and frail patient population, the patient should be placed in the center of treatment decision making, integrating health care providers, patients and their families or caregivers and the risks, burden and benefits of dialysis should be considered versus conservative management, as well as the symptoms and clinical situations that could justify dialysis initiation[40]. The advantages and disadvantages of the modalities of dialysis should be discussed with each patient taking into consideration each patient unique goals and priorities[40].

Knowing that dialysis can not necessarily increase lifespan neither the years with good quality of life, a patient may prefer to deal with his symptoms and opt for a free life to travel and socialize, instead of spending the rest of his life in exhausting treatments[23,40].

Taking into account the morbidity and the impact in life quality, older adults may prefer to postpone dialysis until it is definitely needed or should prefer a conservative treatment[40].

Rosansky and co-authors provided a framework for management of advanced CKD in older adults (Figure 2*, appendix*)[40].

The authors assumed that the competing risk of death from non-renal causes due to comorbidities and a slow loss of renal function, < 3 ml/min/1.73 m^2/year of eGFR, makes the likelihood of dialysis need low[40].

High comorbidity and a poor functional status may be eliminating factors when considering dialysis as an advantage for survival[42–45].

After the discussion about the pros and cons of dialysis initiation, the patient may choose a non-dialytic conservative management that can include all CKD therapies as well as palliative care, prioritizing the patient comfort and symptom relief[40].

6 Particularities of The Renal Replacement Therapy for Frail and Comorbid CKD Patients

If after the decision-making process, it is decided to start dialysis treatment, any of the dialysis modalities will affect the day-to-day life of the patient and their family and will bring major or minor complications[46]. Therefore, delivery of dialysis, for comorbid and frail CKD patients population should focus on improving symptoms, minimizing complications, maintaining or improving physical, mental and social activities to return to their normal activities instead of merely extending life or postponing death[46].

Certainly, a frail older patient with a low muscle mass, low food intake, low physical activity, will not require the same dialysis dose as a younger and more physical active patient[46]. For example, as a domiciliary therapy, the dialysis burden in peritoneal dialysis can be minimized by reducing the dialysis frequency to 5-6 days/week, reducing number of dialysis exchanges on continuous ambulatory peritoneal dialysis (CAPD) to 2-3/day, and limiting daytime exchanges on automated peritoneal dialysis (APD) to the last fill on the cycler[46].

In such therapy plan, routine clearance measurements, such as the collection of 24h urine volume and dialysate samples, may be spared due to the extra burden it represents, once there is no validated small solute clearance target for this patient population[46]. The same applies to questionable laboratory therapy targets in hemodialysis of elderly or frail patients. The treatment of secondary hyperparathyroidism and hyperphosphatemia as well as dietary phosphorus restriction are preventive measures that can be relaxed or even discontinued[39]. Also higher hemoglobin targets and a more liberal use of erythropoietin-stimulating agents reduces transfusions and improves quality of life, although do not reduce mortality and may increase the risk for stroke[39].

A critical decision that must be tailored to the patient is related with dialysis access management: its type and timing of surgical procedure. Older patients frequently need painful vascular access procedures and, as the arterio-venous fistula for hemodialysis is recommended to be anticipated some months before dialysis induction, and the progression to kidney failure is often slower in elderly patients, probably some of them will die before the access usage[42,47]. A central venous catheter dialysis access can be a way to minimize some of the vascular access related discomfort, manly for patients with high comorbidity and short life expectancy[47]. On the other hand, exchanging a tunneled hemodialysis catheter to an arteriovenous graft may reduce the risk for infection[39]. As for the peritoneal access, it can be implanted safely and more shortly in advance of dialysis need (15 days) or even as urgent-start, immediately after the surgical procedure.

Peritoneal dialysis (PD) seems to be a good choice for older adults, with a benefit in survival in the transition to dialysis and in the first years, reducing the risk of emergency hospitalization[48]. Home performed PD can avoid continuous and exhaustive trips to and from the hospital, have less lifestyle modifications and better preserve residual renal function with less hemodynamic stress during treatment; moreover, there is no need for vascular access[48]. However, for those who are very old and with several comorbidities and functional impairment, conservative treatment is a reasonable option[48].

PD, that can be performed at home, is another option for those patients whose primary goal is "freedom from pain". Notably, besides pain, hemodialysis can bring accelerated functional and cognitive declines as well as post dialysis fatigue[42,49].

7 Dialysis vs Conservative Treatment

However, having an advanced CKD does not necessarily mean that the patient needs dialysis treatment. More important than any single eGFR measure value, is in fact, the renal function decline (RFD) evolution throughout time[40]. A slow RFD corresponds to < 3 ml/min/1.73 m^2/year, a medium RFD corresponds to 3-5 ml/min/1.73 m^2/year, and a fast RFD corresponds to ≥ 5 ml/min/1.73 m^2/year. Most older adults with advanced CKD have a slow RFD, meaning that they lose renal function slowly, and many have it stable for several years[40].

As important to estimating RFD, is the assessment of patient's level of comorbidity, to predict if the patient will face a dialysis decision[40]. For example, a 75 year old patient with estimated 3.5 year survival, with a starting eGFR of 25ml/min/1.73 m2 and a fast RFD will probably face the need of dialysis. However, if this patient has a slow RFD, it is unlikely to require dialysis decision[40].

To the patients with low comorbidity levels and more than 3 years of predicted survival, all renal failure treatment modalities should be offered, including renal transplantation[42]. On the other hand, patients with three or six months expected mortality may be candidates for non-dialytic conservative treatment[40,42].

After the clinician has estimated the risk of a future dialysis approach, this forecast must be presented to the patient in order to include him in the decision-making process. A patient with high levels of comorbidity and poor functional status may prefer not to undergo RRT and opt by a conservative management. A conservative approach can include all CKD treatments other than dialysis, psychosocial and spiritual support and symptoms management and it is also possible to incorporate a palliative care approach, more focus on drug therapies to symptoms relief, than exhaustive lab monitoring of lab parameters[40].

Hemodialysis may be a life-saving treatment in acute conditions of renal failure, but is unlikely to provide a survival advantage to a population with a high comorbid burden[40,42].

A conservative management may also be appropriate for patients who do not have comorbidities but who prioritize years with quality of life instead life-extending treatments.

These patients may prefer exchange months or years of life for more personal freedom, in particular, considering that a substantial part of their remaining life will be spent on dialysis and dealing with its complications[42].

8 COMORBIDITY MEASUREMENT INDICES

Given the impact that comorbidity has on patient and disease management/treatment decision, it is important to have measurement instruments to assess overall health conditions, collecting comorbidity information into a single score, instead of evaluating each disease separately[50]. This kind of patient analysis through comorbidity indices, allows the summarizing of multiple conditions and their health impact into a single numeric score, being possible to compare comorbidity between patients[50].

The comorbidity measurement indices can thereby be used as risk assessment tools to predict poor health outcomes, such as, reduced quality of life, frequent hospitalization, readmission, functional decline and mortality[51–55].

Risk assessment tools may be divided into risk scores and risk prediction models, both of which are normally developed using multivariable analysis of risk factors leading to a specific outcome[56]. Risk scores attribute a weight to risk factors/conditions that are independent predictors of an outcome; the weight of each factor is often determined by the value of the regression coefficient in the multivariable analysis[56]. As result, the sum of the weightings in the risk score is associated with increasing risk[56]. Risk scores stratify patients on a scale allowing comparisons with others. Risk prediction models calculate the individual patient risk by entering the patient's data into the multivariable risk prediction model. Risk prediction models are more accurate in predicting an individual patient's risk than risk scores. However, they are more complex to use in routine clinical practice[56].

8.1 VALIDITY AND RELIABILITY OF MEASUREMENT INSTRUMENTS

A comorbidity index should be carefully chosen to ensure the accuracy of the outcome's measurement. The quality of the results provided by an index depends on psychometric properties, such as reliability and validity.

8.1.1 RELIABILITY

Reliability represents the overall consistency of a measure. Is the capacity to reproduce a consistent result in time and space, or from different operators, representing coherence, stability, equivalence, homogeneity and accuracy[57].

An important fact is that, reliability depends on the function of the instrument, the population in study, the circumstances, the context, therefore, the same tool may not be considered reliable under different conditions[57].

The three main reliability criteria are stability, internal consistency, and equivalence.

- Stability measures how similar the results are when measured at two different times, estimating the consistency of measurement repetition. Stability assessment can be performed using test-retest method such as the intraclass correlation coefficient (ICC)[57].
- The internal consistency, or homogeneity, shows if all subparts of an instrument measure the same characteristic and can be assessed by Cronbach alpha or Kuder-Richardson statistical tests[57].
- Equivalence represents the degree of concordance between the results, obtained by two or more observers, regarding a measurement instrument. Different operators should obtain the same final score[57].

8.1.2 VALIDITY

Validity ensures that a given tool measures exactly what it is supposed to measure.

The three main types of validity are content validity, criterion validity and construct validity[57].

- Content validity refers to the adequacy and relevance of an item to measure what is supposed to measure. For example, a tool to measure the satisfaction at work should assess work satisfaction, as well as, other variables related to it, such as, salary, promotions, relationship with co-workers, among others[57].

No statistical test exists to assess specifically the content validity. In alternative, the researchers use a qualitative approach, through the assessment of an experts committee, and then, a quantitative approach using the content validity index (CVI)[57].

- Criterion validity is the correlation of the result obtained with a certain instrument with the result obtained with some other test (criterion variable) that measures the same outcome in study, that is, evaluates how well a test can predict a concrete outcome. The criterion variable should be ideally a *goldstandard* method of measurement that is widely used and accepted in the field[57].

  The evaluation of the validity is achieved by calculating the correlation between the results of both instruments. If a high correlation exists, it will indicate that the instrument in study is measuring what it intends to measure[57].
- Construct validity is the degree to which a group of variables really represents the construct to be measured. A construct represents a concept or feature that can be observed, but can be measured by observing other characteristics that are associated to it[57]. This type of validity is not commonly tested using comorbidity indices[50].

Researcher must remember that reliability and validity are not fixed qualities, and can vary depending on the circumstance, population, type and purpose of the study[57]. This is important to critically evaluate studies comparing different scores.

8.2 Risk Assessment Scores in Different Clinical Fields

Different risk assessment scores are used in the clinical practice of different clinical fields.

The American Society of Anesthesiologists (ASA) physical status classification system was developed to offer clinicians a simple categorization of a patient's physiological status that can help predict operative risk[58]. Anesthesia providers use this risk stratifying score to access patient’s preoperative comorbid conditions to help decide if a patient should have a surgery. For predicting operative risk, other factors to consider include age, comorbidities, extent, and duration of the operative procedure, planned anesthetic techniques, the skillset of the surgical team, duration of surgery, available equipment, blood products needed, medications, implants needed, expected postoperative care[58]. Underlying fitness is an important predictor of survival after surgery, for example, a high ASA score is predictive of both increased postoperative complications and mortality after non cardiac surgery[56].

CHA_2-DS_2-VASc score or the Grace score are examples of risk-stratifying measurements used in cardiology. CHA_2-DS_2-VASc is a risk score used to predict stroke risk in patients with atrial fibrillation. CHA_2-DS_2-VASc score parameters are congestive heart failure, hypertension, age above 75 years old, diabetes mellitus, previous stroke or thromboembolism, vascular disease, age between 65 to 74 years and sex, each one with a corresponding weight[59]. The higher the total score, the higher the stroke risk[59].

The Grace score provides a widely applicable method of assessing the risk of both mortality or reinfarction during the hospital stay and at 6 months after discharge following an acute coronary syndrome episodef[60]. Grace score evaluated parameters are age, Killip class, systolic blood pressure, presence of ST-segment deviation, cardiac arrest during presentation, serum creatinine concentration, presence of elevated serum cardiac biomarkers and heart rate[60].

In gastroenterology, Child–Pugh and Model for end-stage liver disease (MELD) scores have been widely used to predict the outcomes of cirrhotic patients. The first version of Child–Pugh score included ascites, hepatic encephalopathy, nutritional status, total bilirubin, and albumin.

It was later modified by Pugh by adding prothrombin time or international normalized ratio (INR) and removing nutritional status. Child–Pugh score is used to assess the severity of liver dysfunction in clinical practice[61].

MELD score was made to predict the survival of patients undergoing transjugular intrahepatic portosystemic shunts. This score includes total bilirubin, creatinine, and INR and is used to stratify the priority of liver transplantation candidates[61].

In gastroenterology the two most used upper gastrointestinal bleeding risk stratification scores are the Rockall and Glasgow Blatchford scores[62]. Rockall score was designed to predict mortality. The parameters Rockall score are age, shock, comorbidities and the diagnosis and presence for stigmata of recent hemorrhage at endoscopy[62]. This score relies on endoscopic findings, its use at initial patient assessment is limited.

The Glasgow-Blatchford score was derived seven years later to identify patients who needed treatment and considered urea, hemoglobin, systolic blood pressure, heart rate, presenting features and comorbidity[62].

These examples underlie that scores are used specifically and dynamically according to the objectives, its feasibility and the state of art.

8.3 Comorbidity Measurement Indices in Nephrology

Although, in young patients the benefits of RRT outweigh the risks, the same is not true for older and frail patients with comorbidities other than CKD[63]. It was shown that in patients with end-stage CKD, who are elderly or have a high comorbidity burden, RRT not always improves health- related quality of life or enhances survival, since their multiple comorbidities tend to worsen after dialysis initiation as well as their functional status[63]. Even with RRT, the life expectancy predicted for these patients, may be as low as 8 months and the risk of mortality varies between 20-60% when compared with chronic dialysis patients without comorbidity[64].

Therefore, risk stratification scores are extremely important to discriminate the patients with poorest prognosis before initiating dialysis. Parameters such as age, comorbidity, functional status and time to reference to dialysis can be used to calculate risk stratification scores[15,65].

8.4 Charlson Comorbidity Index

The Charlson comorbidity index (CCI) was first described in 1987 and was based on the mortality data in 1 year, of 607 patients admitted in medical service during a month period in 1984[66]. The authors intended to develop a method for the classification of comorbidities that could disguise the risk of mortality, to be used in longitudinal studies. In this index, sixteen diseases were included, each one having a different weight, depending on their association to mortality[66]. The total score in the CCI is derived by summing the assigned weights of all comorbid conditions[66] (Table I*, appendix*).

CCI is the most widely used tool to measure co-existing health conditions and it has been validated for predicting with good accuracy the risk of mortality, disability, hospitalization, and length of hospitalization stay, emergency department visits and utilization of different healthcare services in various disease subgroups[51,64,67–70]. The widespread use of this index could be explained by the fact that it is not designed for patients with a specific medical condition, is easy to use and can be assessed using routine healthcare data extracted from electronic health registries for risk stratification[36,71,72].

Updating in the CCI was done since its baseline creation, accommodating knowledge advances.

The Charlson/Deyo measure is an adaptation of the original CCI[52] that includes in this variant the 17 diagnoses by using ICD-19-CM codes from administrative data[52].

Quan and collaborators argued that with advances in the effectiveness of treatment and disease management, the contribution of comorbidities found within the CCI to mortality was likely to have changed since its development in 1984. The authors reevaluated the Charlson index and reassigned weights to each condition by identifying and following patients that had in-hospital mortality. The "Charlson index modified by Quan." was applied to hospital discharge data from 6 countries and showed the ability to predict in-hospital mortality[73]. In "Charlson index modified by Quan", only 12 comorbidities were retained as compared with 17 conditions in the original Charlson index. The updated index discriminated mortality well in the testing population and 6 validating external databases[73]. The authors conclude that 5 of the 17 comorbidities of original CCI, were not associated with mortality in 1 year follow-up period, therefore they were eliminated from the updated index (myocardial infarction, peripheral vascular disease, cerebrovascular disease, peptic ulcer disease, and diabetes without chronic complications)[73]. However, other disease weights have increased compared with original CCI (congestive heart failure, dementia, mild liver disease, and moderate or severe liver disease) and others have decreased (diabetes with chronic complications, renal disease, and AIDS/HIV)[73]. The weights of Chronic pulmonary disease, rheumatologic disease, hemiplegia or paraplegia, any malignancy, and metastatic solid tumor, remained unchanged[73]. The maximum score for a patient was 24 according to the updated scoring method as compared with 29 for the previous Charlson index[73].

Banay et al., showed that CCI can also be adapted to be used with medico-administrative databases as they did with the French National Health Insurance, using ICD-10 codes, to predict 1-year mortality of discharged patients. This study was the first to adapt CCI to a large database including more than 6 million of inpatients[71].

8.4.1 Age-adjusted Charlson Comorbidity Index

Because age has been determined to influence survival, the CCI was modified by Charlson et al. in 1994[74]. This modification, the age-adjusted Charlson comorbidity index (ACCI), includes the age of the patient as a correction variable of the final score of the Charlson index. This adapted index is identical to the original CCI, with the exception that 1 point is added for each decade of age over 40 years old[74]. So, age and comorbidity independent risks have been combined to estimate the risk of death, having both variables substantial impact on long term survival[74].

Charlson and collaborators suggested that if the study is large, both age and comorbidity can be examined separately. However, If the study is relatively small, it would be helpful to have a method of combining them into a single variable[74].

In recent published studies, ACCI has been shown to outperformed the original CCI [75–79].

8.4.2 Charlson Comorbidity Index in Nephrology

Several comorbidity indices have been validated in renal populations, being the CCI, the most notable and widely used. One advantage for nephrologists, is that many comorbidities present in CKD patients are covered by CCI (for example, cardiac diseases and diabetes). On the other hand, comorbidities are scrutinized in advance of nephrology therapy plan so can be reliably registered by the nephrologist in their databases.

Several works showed the capacity of CCI in predicting mortality in nephrology field.

Talib and collaborators, shown that the CCI could be used as a predictor of outcome in critically ill patients with acute kidney injury (AKI). They showed that CCI greater of 6 independently predicts in-patient mortality and poor renal outcomes in these patients[53].

Other study examined the predictive role of CCI on mortality of patients with type 2 diabetic nephropathy[80]. The impact of CCI on mortality was assessed by the Kaplan-Meier analysis, showing that the mortality increased with CCI scores: 21.0% in patients with CCI scores of 1-2, 56.7% in patients with CCI scores of 3-4, and 22.3% in patients with CCI scores ≥5[80]. Moreover, the authors consider that CCI provides a simple, readily applicable, and valid method for classifying comorbidities and predicting the mortality of patients with diabetic nephropathy, allowing an earlier and more effectively patients identification and treatment[80].

Another study aimed to recalibrate and validate CCI in Korean incident hemodialysis patients[81]. They developed a modified CCI (mCCI) in incident hemodialysis patients (mCCI-IHD), to improve risk stratification for mortality[81]. The authors assumed that the weights assigned to comorbidities to predict mortality may vary based on the type of index disease and advances in the management of comorbidities[81]. The mCCI-IHD included 14 comorbidities with re-assigned severity weights. They conclude that the mCCI-IHD facilitates better risk stratification for mortality in incident hemodialysis patients compared with the CCI, suggesting that it may be a preferred index for use in clinical practice and the statistical analysis of epidemiological studies[81].

Moore and collaborators compared the performance of 7 established comorbidity scores, including CCI, in predicting mortality after kidney transplantation. The results suggested that the models based on the Recipient Risk Score and the CCI showed the best fit[82].

Other studies showed the capacity of CCI in predicting hospital readmission. Lin and collaborators assessed the association between CCI scores, obtained in a population of patients receiving dialysis, both hemodialysis and PD, and the unplanned readmission following the hospital discharge within 30 days[51]. The authors conclude that higher CCI was associated with an increased risk of 30-day readmission in patients receiving hemodialysis or PD, and could be used for risk-stratification/clinical risk prediction and patient management[51]. Also, Luisa et al., evaluated the correlation between the CCI and hospital admissions and mortality in stage IV CKD patients with similar conclusion that CCI is a strong predictor of mortality and hospitalization in this patient's population and can be used for risk stratification in clinical practice[65]. The authors highlighted that the CCI is a quick, easy, and convenient score that can help clinicians on daily practice, useful for making the decision to start dialysis or not[65]. This study also conclude that the higher the CCI, the lower will be the survival analyzed by Kaplan-Meir analysis[65].

8.4.2.1 Charlson Comorbidity Index Adaptations for End-Stage Renal Disease Patients

The relevance of CCI is that, it is the most widely used score in the clinical practice to assess survival in different patient populations, with different diseases and in patients with ESRD, not being disease-specific[64,76,78,83–85]. This does not excludes attempts to create comorbidity scores to specifically predict outcomes in ESRD patients[44,86–88] and also to document limitations in its accuracy to address complexity in CKD patients and on dialysis[89].

The French Renal Epidemiology and Information Network (REIN) database has been used to develop scores to establish the 6-month prognosis and to improve the patient centered care, as well as to help in decision-making at dialysis start in eldery ESRD patients[90].

Recently, Pladys and coauthors, developed and validated a simple comorbidity score to predict the one-year mortality in patients with ESRD[91]. Their results suggested that the comorbidities recorded at dialysis start in the Renal and Epidemiology Information Network (REIN) database, is sufficient to construct a score to predict the one-year mortality risk before dialysis initiation, helping clinicians to identify high risk patients and allowing the improvement of personalized management[91]. This new score (Rennes score) has been established using only five comorbidities (cardiac diseases, respiratory insufficiency, hepatic disease, active malignancy, walking disability), one laboratory parameter (albumin level) and age at dialysis start[91]. As no dialysis-dependent parameter item was retained, this score can be calculated even before dialysis initiation[91]. The Rennes score did not include Diabetes as a variable, because the authors conclude that diabetes was not significantly related with the risk of death[91]. This conclusion could be explained by the improvement in diabetes treatment observed in the last decades, making this condition no longer considered as a major risk of death for dialyzed patients[91]. In comparison to CCI, the authors conclude that Rennes score outperforms CCI[91].

Controversially, although CCI widespread utilization, McArthur and collaborators, conclude from a comparative study of five comorbidity indices (CCI, ESRD-CCI, John Hopkins ACG score, Elixhauser score and Wright-Khan index) to predict 1-year mortality in CKD patient, that these existing comorbidity indices need to be modified with additional risk factors to improve their performance in CKD, or a new index should be developed for this population[92]. The authors made suggestions for different subpopulations: in kidney transplant recipients, the inclusion of transplant-specific factors known to be associated with posttransplant mortality, such as donor characteristics, time on dialysis, and pretransplant panel reactive antibody score, could provide substantial gains when predicting transplant recipients at greatest risk for mortality after transplantation; in patients receiving dialysis factors such as modality, access type and cause of kidney failure could be incorporated in the scores for a more accurate mortality prediction[92].

Even the inclusion of laboratory test results routinely used to predict the progression of kidney disease and mortality in patients with reduced kidney function, could increase the accuracy of mortality-risk prediction in CKD patients population[92]. These studies testimony the progressive, always demanding pursuit of risk stratification in chronic diseases.

Gomez et al., suggested that although there are limitations with most used CCI, it is important to acknowledge that it retains validity and there are features that make it valuable[89]. CCI is very intuitive, easy to use and the comorbid conditions that are expected to confer a higher risk of mortality are weighted more heavily (with exception of HIV that nowadays have a lower mortality rate)[89]. Besides, it remains as a tool used in other clinical fields often overlapping CKD, cardiac, infectious and oncological diseases.

8.4.3 Charlson Comorbidity Index in other clinical fields

Kim et al., aimed to determine the prognostic value of CCI with regard to mortality of patients with myocardial injury after non-cardiac surgery (MINS)[85]. The authors conclude that high CCI score was associated with increased 30-day mortality in patients with MINS, suggesting that the CCI may need to be considered when predicting outcomes of MINS patients[85].

Poupin and collaborators aimed to evaluate mortality, appropriate implantable cardioverter-defibrillator (ICD) therapy rates and survival gain in an elderly population after risk stratification according to the CCI[93]. The authors conclude that elderly patients with CCI score ≥ 4 had the lowest survival after ICD implantation and little survival gain in case of appropriate defibrillator therapy[93]. More than age alone, the burden of comorbidities assessed by the CCI could be helpful to better select elderly patients for ICD implantation[93].

Minol and colleagues, evaluated the risk-predictive value of the age-adjusted Charlson comorbidity index (ACCI) in the setting of minimally invasive mitral valve surgery[75]. Patients with an ACCI ≥8 have a very high surgical risk, with a significant increase of mortality as well as other adverse events and should receive very careful attention[75]. Another study concluded that AACI has significant predictive value for clinical outcome and could be useful in estimating outcome in heart failure patients[94]. A higher ACCI was associated with more advanced NYHA class, HFpEF, a lower BMI, higher urea and lower eGFR, sodium, hemoglobin and albumin[94]. A higher ACCI was associated with less therapy with RAS blockers but with more furosemide therapy[94].

Bonaventura and collaborators evaluated whether ACCI could predict complications (including surgical complications, intensive care unit [ICU] admission, and in-hospital death) among patients undergoing cholecystectomy for acute cholecystitis[78]. The authors conclude that ACCI greater than 5 was found predictive for in-hospital complications[78]. In patients surgically treated for acute cholecystitis, ACCI could represent an additional tool, along with available risk scores, to help surgeons in choosing the best therapeutic option[78].

A recent study concluded that CCI can be used to predict poor outcomes in COVID-19 infected patients[95]. Compared to a CCI score of 0, a CCI score of 1-2 and CCI score of ≥3 was prognostically associated with mortality and poor outcomes[95]. Per point increase of CCI score also increased mortality risk by 16%[95]. Moreover, a higher mean CCI score also significantly associated with mortality and disease severity[95]

Qu and co-authors used CCI and ACCI to predict overall survival in 268 patients with the Intrahepatic cholangiocarcinoma who underwent liver resection. The authors conclude that ACCI was superior to CCI in predicting overall survival in this patients cohort [79].

Dias-Santos and collaborators evaluated ACCI scores in 497 pancreatic cancer patients who underwent curative resection[76]. This study concluded that a ACCI >4 was a predictor of postoperative complications, increased duration of hospital stay, and mortality within 1 year of pancreas resection[76].

CCI value ≥6 was found to be associated with the significantly shorter overall survival in patients with resectable sinonasal tract squamous cell carcinoma, functioning as a prognostic factor in cases of resectable sinonasal tract squamous cell carcinoma[96].

Yang et al., investigated the incidence of comorbidities and the impact on prognosis in a cohort of operated lung cancer patients[97]. They conclude that higher CCI and ACCI scores were associated with a poor 3-year overall survival proving that these scores could be used to classify patients in prognostic groups according to comorbidities[97]. They also conclude that the ACCI score, which includes age, had better discrimination and predictive accuracy for prognosis compared with the CCI and Elixhauser comorbidity index (ECI) scores and could have widespread applicability[97].

In older colorectal cancer patients, CCI was useful to predict postoperative outcomes and shown to be an independent prognostic factor[83]. Tominaga and collaborators showed the overall survival tended to be lower in patients with high CCI scores group[83].

Ho et. Al., evaluate the risk of empyema in patients with COPD after adjusting for age and comorbidities using the ACCI[77]. The authors showed that higher ACCI scores conferred the highest risk and mortality of empyema[77].

Outcomes in chronic myelomonocytic leukemia (CMML) are highly variable and may be affected by comorbidity[84]. A recent study performed in a nationwide population-based cohort of 337 patients, comparing different prognostic scoring systems and comorbidity indices in CMML showed that CCI had the highest C-index and was the only comorbidity index independently associated with survival in multivariable analyses[84]. The authors conclude that we CCI and CMML specific prognostic scoring system (CPSS) have the best prognostic power[84].

Another study concluded that CCI predicts poor outcome in chronic myeloid leukemia patients treated with tyrosine kinase inhibitor[98]. In this work it was examined the usefulness of the CCI for predicting practical outcomes in elderly CML patients with comorbidities by retrospectively evaluating patient complications at initial diagnosis to score the CCI[98]. The authors shown that patients who scored >3 points on the CCI had significantly shorter survival after diagnosis than those who scored <2 points[98].

8.4.4 Charlson Comorbidity Index validity

In terms of validity, the criterion validity, is the most frequent type of validity analyzed in comorbidity indices[50]. Although, no gold standard exists for measuring comorbidity, researchers and clinicians use another comorbidity score as comparison[50].

In most studies, CCI presented moderate to good correlation with other comorbidity indices and with different outcomes[51,64,67–70]. Its reliability and validity have been assessed in different patient populations and overall, its test–retest and interrater reliability is moderate to very good[99]. Moreover, this comorbidity index has been adapted for use with diagnoses from administrative databases, and revised weights have been suggested or adapted for specific populations [64,73,81,91,97,99].

8.5 ELIXHAUSER'S COMORBIDITY INDEX

The Elixhauser's Comorbidity index (ECI) was developed in 1998, works similarly to CCI but includes 30 comorbidities (17 from CCI and 13 new ones)[100]. Elixhauser and collaborators used administrative data to identify the thirty health conditions that had a greater impact on short-term outcomes in acute hospital patients. In comparison to CCI, in ECI no weight is attributed to each comorbidity, assuming that all the health conditions are equally related with the outcomes, which hardly can be true[50]. In this study, ECI appeared to have better performance in all aspects of validity, however the difficulty in collecting thirty health conditions make it less feasible and discourage clinicians and investigators from using it[100]. Besides measuring in hospital mortality, ECI was also used to predict length of stay, adverse events, hospital discharges and hospital readmission[52,54,55,101].

The ECI was later updated by van Walraven et al., that used inpatient admission data from a Canadian hospital, during 13 years, to develop a set of weights for the 30 Elixhauser comorbidities related with in hospital mortality[102]. Each of the 21 Elixhauser comorbidities had a weight assigned, ranging from -7 to 12, with 9 comorbidities assigned with a weight of zero[102] (Table II*, appendix*). Positive score values are related with an increase in the risk of in hospital mortality, and negative score values are related with a decrease in risk of death in hospital[102].

It is important to consider that the comorbidities-associated weights used in the comorbidity scores, may be different between patient's populations (all hospitalized patients vs a restricted cohort), between outcomes (mortality vs hospitalization) and between geographic areas (countries, regions)[103].

Despite being very versatile and more statistically significant than CCI, in predicting the risk of different outcomes, the CCI is still being very used[54,55,101,103].

ECI has been compared to other scores, more commonly to CCI[55,97,103]. In general, ECI tends to have similar or slightly better performance than CCI, however the results can be population, outcome or context dependent[54,55,97,103,104].

In nephrology, there are not as many studies using ECI as there are using CCI. Kimura and collaborators have shown recently that ECI score increased with CKD stage in both general and hospitalized populations, however the median score for CKD stage G3b was 0 in the general population, whereas it was 5 in the hospital population at the same stage[105]. In CKD stage G5, the median comorbidity score was similar between both populations[105].

To address the variability in risk stratification tools, McArthur and collaborators, compared five comorbidity indices (CCI, ESRD-CCI, John Hopkins ACG score, Elixhauser score and Wright-Khan index) to predict 1-year mortality in CKD patient, concluding that these existing comorbidity indices would all improve their performance in CKD, with introduction of additional risk factors related with specific dimensions in this population[92]

8.6 MEDICATION-BASED INDICES

Generally, the number of prescribed drugs is directly related with the number of chronic diseases, therefore medication-based indices are an alternative tool for measuring comorbidities [106].

The Chronic Disease Score (CDS), is a medication-based index, developed in 1992, by Korff and collaborators, to predict health outcomes[107]. Originally it was consisted by 17 diseases with a weighting system assigned and was later updated by Clark *et al.,* to include 28 conditions with a weighting system based on regression models[108].

Due to the pharmacotherapy development over the last thirty years, the original CDS became quite limitative[109].

In 2017, Corrao and collaborators proposed a new method, the Multisource Comorbidity Score, combining pharmaceutical prescriptions and information from hospital discharge records to stratify patients according to their morbidity status[106]. In spite of its more complex variables database, when compared to CCI, ECI and CDS, this new method showed to be better predictor of 1-year mortality[106].

Iommi and co-authors implemented a new version of CDS, the Modified-Chronic Disease Score (M-CDS), using detailed information from the pharmaceutical prescriptions databases that include not only the traditional drug treatments but also the novel pharmacotherapies introduced over the last 30 years as well as the number of drugs taken by the individual[109]. In this studied the predictive ability of M-CDS was assessed using ROC analysis and was compared with CCI and with original CDS predictive ability. The authors concluded that M-CDS, using only drug prescriptions, outperformed CCI in predicting 1-year mortality and was not inferior to the multisource comorbidity score. However, no significant difference was found between M-CDS and original MCS[109].

The authors considered that a possible reason for the lower predictive ability of CCI when compared with M-CDS, could be because the hospital discharge records, used by CCI, are often subject to restrictions on the number of diagnosis recorded, while the drug-based score does not have this limitation[109]. Authors argued that M-CDS has advantages when compared to other indices once it is based on a single data source being unaffected by the variability in diagnostic coding[109], containing a large number of conditions, M-CDS may enable in-depth studies on the interplay between mental and physical disorders[109]

Medication-based indices have the advantage that they can be used when diagnostic data are not available, unreliable, or inconsistent[110]. The medication data reflect the currently treated chronic diseases and might have better predictive values and more reliable, complete, and timely than diagnostic data[110]. Furthermore, in comparison with diagnosis-based indices, the medication-based indices are robust against under documentation of diagnoses[110]

Using only pharmaceutical database instead of using hospital records may decrease the computational workload while capturing the complexity of patients's clinical condition[109].

However, CDS has also its limitations, for example, dementia and geriatric conditions such as immobility, frailty or falls are not treatable with drugs, meaning that part of the disease burden of a patient may go underestimated using a medication-based score[110].

Medication-based scores link patterns of medication prescriptions with selected chronic diseases, however, the selection criteria of diseases are often not transparent and relevant diseases are missing[110]. Moreover, these type of scores based on medication prescriptions can be not up to date, for example drugs are included that are not marked anymore (e.g., isoproterenol, guanethidine, procainamide or disopyramide) whereas new pharmacological therapies with great impact on clinical endpoints of chronic diseases (e.g., angiotensin II receptor antagonist, bisphosphonates for osteoporosis) or monoclonal antibodies in autoimmune diseases are missing[110].

To date, there is no proven superiority in the health status predictive capacity of drug-based indices over diagnosis-based ones[109]. Furthermore, the lack of an updated version of CDS does not allow appropriate performance assessment and comparisons[109].

9 The Multidimensional Approach As Part Of The Decision-Making Process

For an appropriate decision-making process, an accurate prognostic evaluation of CKD older patients is crucial. Given the, comorbidity and frailty present in CKD old patients population, recently, increasing evidences indicates that the prognosis of these patients is correlated with the presence of concomitant diseases and the degree of cognitive, physical, biological and social impairment[111].

According to World Health Organization (WHO), the knowledge about patient's functionality is useful to support, assist and facilitate decision-making in various domains, namely, to establish a diagnosis and prognosis, carry out a clinical judgment, define treatments and care, as well as, detect risk situations, identify areas of dysfunction, monitor functional decline, establish care plans and identify the need to use services[112].

WHO approved the International Classification of Functioning, Disability and Health (ICF), that belongs to the WHO family of international classifications as is the case of ICD-10 (International Statistical Classification of Diseases and Related Health Problems)[112]. ICF classifies functioning and disability associated with health conditions and was created based on the evidence that diagnosis alone does not predict service needs, length of hospitalization, level of care or functional outcomes[112]. WHO defends that if we use uniquely medical classification of diagnoses, we will lack information about levels of functioning and disability, important for health planning and management purposes[112].

In 2019, the Portuguese Health System and *Direção Geral de Saúde,* followed the WHO guidelines and ICF , releasing a guideline for the implementation of the *Tabela Nacional de Funcionalidade* (TNF) in Adults and Seniors[24].

TNF allows the classification of thirty-eight activities and participations, grouped in five dimensions: Mobility and self-care, general skills, specific skills, sociability and handling capacity[24].TNF should be applied to everyone with more than 18 years old, with chronic disease, permanent or temporary disability, whenever the following requirements are met: home care, rehabilitation plan, referral to the national network of integrated continued care, usage of support products, performing biological therapy, performing dialysis on an outpatient basis, home respiratory care, referral to the attending physician whenever there is a change in the user's functionality during the period in which he was in hospital[24].

The application and registration of data in the TNF is performed by health professionals, involved in the provision of health care, in an interview with the patient, where standard questions are asked or patient's acts, activities and attitudes are directly observed[24].

For each of the TNF dimensions, the health professional must identify the facilitating environmental factor or barrier, which may positively or negatively influence the performance of each of the activities and participation under analysis[24].

However, this multidimensional tool demands human and e-health resources whose complexity justifies the delay in its implementation and use by the clinicians.

Geriatricians, frequently use the Comprehensive Geriatric assessment (CGA), a tool of choice to globally assess older patients and plan interventions[113]. CGA is a multidimensional, interdisciplinary diagnostic process, performed by different professionals (geriatrician doctor, nutritionist, social worker, occupational therapist, psychologist…), used to determine the medical, cognitive, psychological and functional capabilities of older persons, with the intention to create a coordinated and integrated plan of treatment and long-term follow-up[113]. CGA can be used for patient's risk stratification, predicting mortality or morbidity risks, treatment-related risk assessment, care planning, and frailty-targeted intervention[113,114].

The Multidimensional Prognostic index (MPI), is a prognostic measurement tool, based on CGA, that uses an algorithm that includes a list of risk factors included in the concept of CGA, such as, nutrition, functional status, mobility, cognition, multimorbidity, polypharmacy and social support[113], to create a numeric score, that represents the global risk of multidimensional impairment of older patients[111].

MPI is calculated from data obtained from CGA, activities of daily living (ADL), instrumental activities of daily living (IADL), short portable mental status questionnaire (SPMSQ), mini nutritional assessment (MNA), Exton-Smith score (ESS) and cumulative index rating scale (CIRCS) in addition to information on medical history and cohabitation[115](Table III*, appendix*).

MPI is nowadays one of the most frequently used measurement, to evaluate frailty and has been showed, in multicenter studies, to be able to accurately predict mortality[116], to predict in-hospital length of stay[117,118], to monitor alterations in health and functional status during hospitalization[119,120], to identify older patients that will be admitted to homecare services, nursing homes and /or re-hospitalized 1 year after discharge[121], to give information about life quality in older patients admitted to emergency department[122], to predict the impact on healthcare resources[123] and good application for disability social benefits in older patients with cognitive decline[124].

So far, MPI has been applied, with great results, in older patients, and showed up as an accurate and well-calibrated prognostic tool, showing very good performance in terms of validity, reliability and feasibility for older patient's management[125–127]. MPI has been applied in acute diseases including heart failure[128], gastrointestinal bleeding[111], pneumonia[111], transient ischemic attach[129] and also in chronic diseases such as CKD[130], diabetes[131], cancer[132], depression[133] and dementia[134].

In the context of a recent European Union co-funded research project named MPI_AGE, that aimed to use MPI to develop predictive guidelines for clinical and management decisions in frail older people with multimorbidity, several clinical studies evaluate the adequacy of some treatments in geriatric population such as, anticoagulation in atrial fibrillation[135], statin in secondary prevention of diabetes[136] and coronary heart disease[137], anti-dementia drugs in late-life dementia[138] or transcatheter aortic valve implantation (TAVI) in older patients with aortic stenosis[139,140] and enteral tube feeding intervention in malnourished hospitalized older patients[141].

Other studies showed that MPI is also useful in the field of personalized therapies such as guiding immunotherapy in cases of advanced malignancies[142], to predict the risk of in-hospital and follow-up complications in patients with acute myocardial infraction who underwent percutaneous coronary intervention[143], in outcome prediction in elderly surgical patients with colon-rectal cancer[144] or to predict non-invasive ventilation failure in elderly with acute respiratory failure[145].

Specifically in nephrology MPI was recently used by Lai and collaborators, who assessed the association between MPI and both hospitalizations and mortality among older adults with renal disease[115]. This study included patients with CKD (stage 3-5 KDOQI) and on dialysis. MPI significantly correlated with days of hospitalization and number of hospitalizations per year, which was higher in MPI grade 2 compared to MPI grade 1 and grade 0. Also, there was a significant association between MPI grades and mortality[115]. The authors considered that MPI has potential to be clinically useful to accurately identify and adequately manage patients with renal disease[115].

Previously, Pilotto and collaborators also have shown, that MPI, and its multidimensional assessment, has an important role in predicting long-term all-cause mortality in older and frail CKD patients[130].The authors conclude that MPI was associated with outcomes in patients with renal disease, suggesting that a multidimensional evaluation should be implemented in this clinical setting[130].

In all these studies, the multidimensional approach, turned out to be a good method to help clinician in the decision-making process, depending on the degree of patient's multidimensional condition[111].

Hansen and collaborators showed that it can be assessed using clinical records[146]. This new version of MPI, the record-based MPI, facilitates MPI calculation directly from electronic medical records, at discharge in hospitalized older patients, and accurately predicted post-discharge mortality (after 90 days and 1 year), hospital readmission risk and is associated with length of hospital stay in older medical inpatients[146].

In an attempt to create a more user friendly and feasible multidisciplinary approach that includes a comprehensive assessment, Couchoud and co-authors proposed a risk stratification algorithm to decide on the appropriate strategy of care for elderly ESRD patients according to their level of risk of early death (mortality during the first 3 months of dialysis)[44]. This algorithm combines prognostic score for early mortality (gender, age, congestive heart failure, severe peripheral heart disease, dysrhythmia, severe behavioral disorders, active malignancy, impaired mobility and serum albumin) with a geriatric assessment, multidisciplinary approach and patient preferences. According to the results obtained in this evaluation a tailored strategy of care can be set up, in which dialysis may or may not be considered[44]. Different modalities of dialysis treatment can be offered, such as nurse-assisted peritoneal dialysis, short or daily hemodialysis sessions at home or in a nursing home, or a markedly reduced dialysis regimen in a dialysis unit[44]. After specific clinical evaluation, renal transplantation may be offered to the low risk group[44].

Figure 3 represents the evolution and dimensions of the different measurement tools addressed in the present work (Figure 3*, appendix*).

Table IV, resumes the advantages and disadvantages of the different measurement tools addressed in the present work. (Table IV, *appendix*).

Although no existing risk stratification score can predict with hundred percent certainty the patient's future condition, validated scores used in clinical practice may improve accuracy of poor outcome or prognostic estimates[90]. Specifically in Nephrology, they may allow evaluation of patients individual burden of disease and facilitate clinician's decision of recommending dialysis treatment to those who may benefit or proposing alternative care that respect patients health condition to those who don't[90].

CONCLUSION

The number of persons undergoing dialysis treatment is increasing worldwide due to a myriad of facts such as, the improved survival of the general population, aging and associated increase in CKD incidence, broadening of kidney replacement therapy inclusion criteria, and greater access to dialysis in low- and middle-income countries and decrease in the mortality rate of dialysis patients.

The majority of patients with CKD are frail and comorbid, with an increasing risk of poor outcomes. In order to give a better treatment to these patients, favoring patients' preferences and needs, and to ensure an adequate resources allocation, patients risk stratification is of extremely importance in the clinical practice and should be advocated.

The present work allowed to conclude that, comorbidity scores such as Charlson Comorbidity Index although simple and deprived from dimensions such as functionality, mental capacity, family and social environment, is validated, reliable and can be of great utility in a bedside and daily usage. CCI allows prediction of renal patients' poor outcomes and patients' risk stratification, important for the decision-making process as well as for adjusting quality indicators in the therapy plan with better resources allocation.

Although multidimensional evaluations allow a more deep and complete understanding of the impact of multifactorial aspects in patient's outcomes, they are time-consuming and demand organization between different health professionals, cross-referencing information between different databases, structured care plans with allocations of dedicated teams within healthcare institutions and will obviously incur costs.

Health policy makers must consider a phased implementation of improvement quality processes, by adopting a simple and user-friendly validated stratification method requested by clinicians in their daily practice, while investing in a more complete and comprehensive method, but extremely complex to implement, also demanding ambitious e-health and organizational resources to execute only the long-run.

This might be an opportunity to accomplish a successful two-directional thinking in health management: not to forget assuring the present while building the future.

APPENDIX

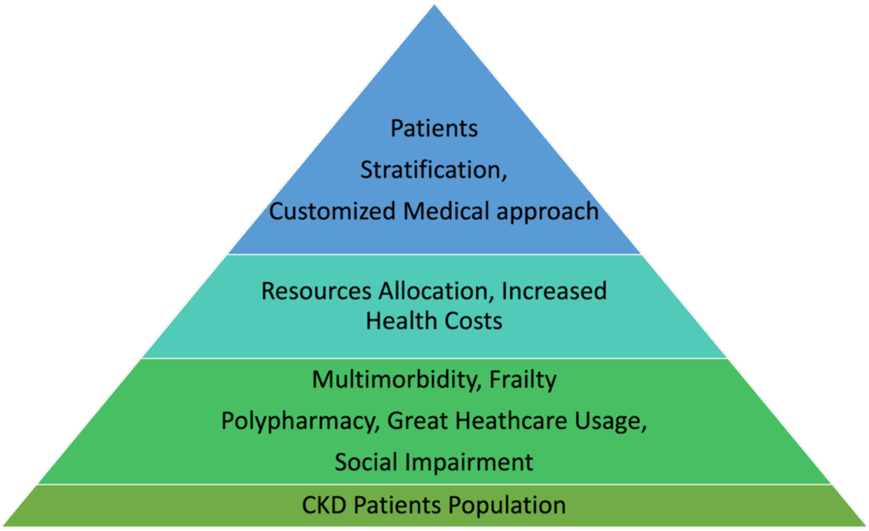

Figure 1 - Illustrative representation of multimorbidity in CKD patients' population and all its inherent aspects.

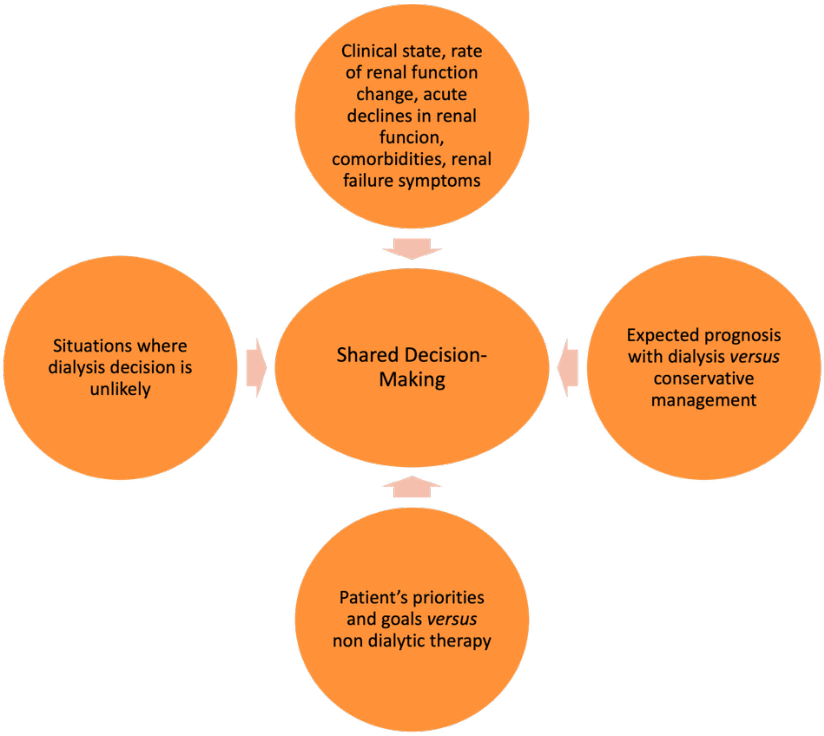

Figure 2 – Framework for management of advanced CKD in older patients. Image adapted from *Rosansky et al., 2017*[40].

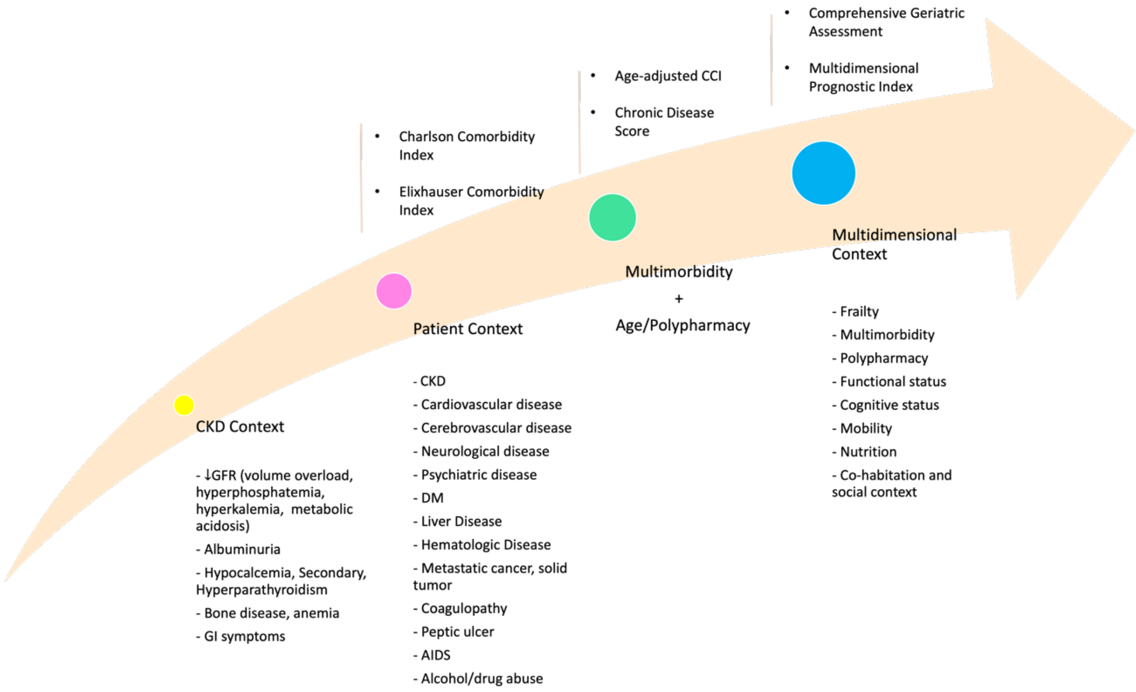

Figure 3 – Illustrative representation of the evolution and dimensions of the different measurement tools addressed in the present work.

Table I: Charlson Comorbidity Index. Table adapted from *Moltó & Dougados 2014*[50].

Charlson Comorbidity Index	
Disease	**Points**
Myocardial Infarction	1
Congestive Heart Failure	1
Peripheral Vascular Disease	1
Cerebrovascular Disease	1
Dementia	1
COPD	1
Connective Tissue Disease	1
Peptic Ulcer Disease	1
Diabetes Mellitus	1 (if uncomplicated) 2 (if end-organ damage)
Moderate to severe CKD	2
Hemiplegia	2
Leukaemia	2
Malignant Lymphoma	2
Solid Tumor	2 6 (if metastatic)
Liver Disease	1 (if mild) 3 (if moderate to severe)
AIDS	6

Table II – Elixhauser Comorbidity Index modified by Walraven and collaborators. Table adapted from *Walraven et al.2009*[102].

Elixhauser Comorbidity Index	
Disease	**Points**
Congestive Heart Failure	7
Cardiac arrhythmias	5
Valvular Disease	-1
Pulmonary circulation disorders	4
Peripheral vascular disorders	2
Hypertension	0
Paralysis	7
Neurodegenerative disorders	6
Chronic pulmonary disease	3
Diabetes, uncomplicated	0
Diabetes, complicated	0
Hypothyroidism	0
Renal failure	5
Liver disease	11
Peptic ulcer disease, no bleeding	0
AIDS/HIV	0
Lymphoma	9
Metastatic cancer	12
Solid tumor without metastasis	4
Rheumatoid arthritis/collagen vascular diseases	0
Coagulopathy	3
Obesity	-4
Weight loss	6
Fluid and electrolyte disorders	5
Blood loss anemia	-2
Deficiency anemia	-2
Alcohol abuse	0
Drug abuse	-7
Psychosis	0
Depression	-3

Table III – Multidimensional Prognostic Index. Image adapted from *Pilotto et al., 2012*[130]. ADL- activities of daily living; IADL - instrumental activities of daily living; SPMSQ - short portable mental status questionnaire; MNA - mini nutritional assessment; ESS - Exton-Smith score; CIRS - cumulative index rating scale.

Multidimensional Prognostic Index	
Domain	**Score**
ADL (score)	
6-5	0
4-3	0.5
2-0	1
IADL (score)	
8-6	0
5-4	0.5
3-0	1
SPMSQ (score)	
0-3	0
4-7	0.5
8-10	1
CIRS (score)	
0	0
1-2	0.5
≥ 3	1
MNA (score)	
≥ 24	0
17-23.5	0.5
< 17	1
ESS (score)	
16-20	0
10-15	0.5
5-9	1
Number of Medications	
0-3	0
4-6	0.5
≥ 7	1
Co-habitation Status	
Living with family	0
Institutionalized	0.5
Living alone	1

Table IV - Advantages and disadvantages of the different measurement tools. CCI – Charlson Comorbidity Index; ACCI – Age-adjusted Charlson Comorbidity Index; ECI - Elixhauser's Comorbidity Index; CDS - Chronic Disease Score; CGA - Comprehensive Geriatric assessment; MPI - Multidimensional Prognostic index.

Patient Context

<table>
<tr><th></th><th>PROS</th><th>CONS</th></tr>
<tr><td>CCI
ACCI</td><td>- Simple, quick and easy to use on daily practice;
- Data easily accessed and collected from electronic health registries;
- Reliable; Validated in CKD</td><td>- Only takes in account comorbidity (+/- Age);
- Lack of multidimensional evaluation</td></tr>
<tr><td>ECI</td><td>- More statistical significant than CCI;
- Data collected from administrative registries</td><td>- More difficult; Less feasible;
- Collect 30 health conditions;
- Not often used in CKD</td></tr>
<tr><td>CDS</td><td>- Simple and easy to use;
- Based on medication prescriptions databases;
- Unaffected by variability of diagnostic coding;
- Can be used when diagnostic data are unavailable, unreliable or inconsistent;
- Medication data reflects the currently treated chronic conditions; thus may be more reliable, complete and timely than diagnostic data;
- Requires less computational workload</td><td>- Limitative due to pharmacotherapy development;
- Part of disease burden may go underestimated, due to some geriatric conditions (immobility, frailty or falls) or dementia may not be treatable with drugs;
- Relevant diseases may be missed;
- Not up to date (inclusion of drugs that are no longer used, whereas new drug therapies and monoclonal antibodies are missing)
- Depends on adequacy of medical prescription (e.g. oral hypoglycemic drugs in pre-diabetic, ASA in arteriosclerosis)</td></tr>
<tr><td>CGA</td><td>- Allows global assessment of old patients;
- Determines medical, cognitive, psychological and functional capabilities</td><td rowspan="2">- Complex; Time-consuming;
- Not feasible on daily practice;
- Less accessibility of data;
- Data access and management requires multidisciplinary intervention (multiple professionals, multiple databases)
- More resources and technical expertise needed
- More costs implicated</td></tr>
<tr><td>MPI</td><td>- Measures the global risk of multidimensional impairment;
- Determines nutrition, functional status, mobility, cognition, multimorbidity, polypharmacy and social support;
- Accurate and reliable;
- Data collected from clinical records
- Validated in CKD</td></tr>
</table>

Multidimensional Context

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