Validation of ERBP Guideline Algorithm for Management of Older Patients with Advanced CKD: A Commentary

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The global population is aging. In 2015, over 900 million people were aged 60 or more (12.3% of the population) and by 2050 these numbers are predicted to rise to 2.1 billion and 21.3% respectively[1]. This increase in life-expectancy is most encouraging, but also presents significant challenges. Older age is accompanied by a high prevalence of long-term medical conditions, disability, frailty and dependency, all of which can impair the quality of life of both patients and carers, and impact on health and social services[2,3]. In parallel with all this, the global prevalence of chronic kidney disease (CKD) in older people is also high[4] and these patients experience high levels of co-morbidity, frailty and physical and cognitive dysfunction[5,6].

Though the prevalence of CKD Stage 3 and 4 is high in older people, the rate of progression of the condition tends to be slow[7-9]. Moreover the high mortality rate in these patients, particularly related to cardiovascular causes, tends to pre-empt the development of end-stage kidney disease (ESKD) in a high proportion of patients[8]. This is starkly illustrated by the findings of a large registry study[10], in which the prevailing eGFR level, below which the risk of ESKD exceeded the risk of death, was 15 ml/min per 1.73 m^2 for 65 to 84 year olds, whilst in older patients the risk of death always exceeded that of ESKD. These findings present a number of dilemmas in relation to the management of advanced CKD in the older patient. The dominant concerns in this setting revolve around shared decision-making with respect to referral for consideration of renal replacement therapy (RRT) and in relation to the choice of RRT and conservative management[11]. The importance of shared decision-making is universally accepted, but patients' narratives suggest it is poorly implemented in this setting[12]. The recent European Renal Best Practice (ERBP) Clinical Practice Guideline on management of older patients with advanced CKD addressed these issues[13].

Figure 1 depicts an algorithm outlining the management pathway for older patients with advanced CKD (eGFR < 45 ml/min/1.73m^2), which was proposed in the ERBP guideline. The purpose of the algorithm was to generate information to guide shared-decision making discussions with patients and their carers. The main elements of the algorithm comprise 1/ Establishing the risks of mortality within the next 5 (and 2) years using a validated equation (Bansal et al[14]); 2/ Establishing the risks of progression to ESKD in the next 1, 2 and 5 years using the validated Kidney Failure Risk Equation (KFRE) (Tangri et al[15]); 3/ For patients whose mortality is judged to be very high on the basis of their Bansal score and/or a high level of frailty as indicated by a validated method, and who have a lower risk of developing ESKD as judged by their Tangri score, management recommendations should reasonably be focused on preparations for supportive/palliative care, rather than referral for discussions about RRT; 4/ For patients whose scores indicate a low risk of progression to ESKD (and whose mortality risk is relatively low), management recommendations should focus on preservation of residual kidney function, rather than referral for discussions about RRT; 5/ For those whose scores indicate a high risk of progression to ESRD, management recommendations should include referral for discussion about the choice of preparation for RRT or conservative management. Mortality risk as indicated by the Bansal score should inform these discussions. For patients whose eGFR < 15 ml/min/1.73m^2, use of the validated REIN study equation[16] which predicts 6 month mortality following dialysis initiation, could also provide useful information. It should be emphasised that the ERBP algorithm does not stipulate absolute values of risk. Individual patients have different thresholds for the attribution of "high" risk. These relate to their particular circumstances and inform their treatment preferences, which are an important input into shared decision-making discussions.

A recent publication has attempted to validate major aspects of this algorithm[17] in a subset patients from the Norwegian HUNT study. The study cohort consisted of 1188 patients, aged ≥ 65 years, all of whom had an eGFR < 45 ml/min/1.73m^2. The follow-up period was 5 years. Since the Bansal and KFRE equations were developed and validated in different study populations, it is not known whether they are well calibrated in the same study population. Hence the study sought to validate the performance of each equation in this setting and to evaluate their concurrent use in this cohort to determine how risk of death and ESRD compared. An additional aim was to assess, using Decision Curve Analysis, the clinical impact of this referral algorithm in comparison to algorithms from other guidelines, across a range of possible patient valuations of risk and benefits [18]. Rigorous evaluation of guideline flowcharts is exceptional, so the authors should be heartily congratulated for having conducted this very relevant exercise.

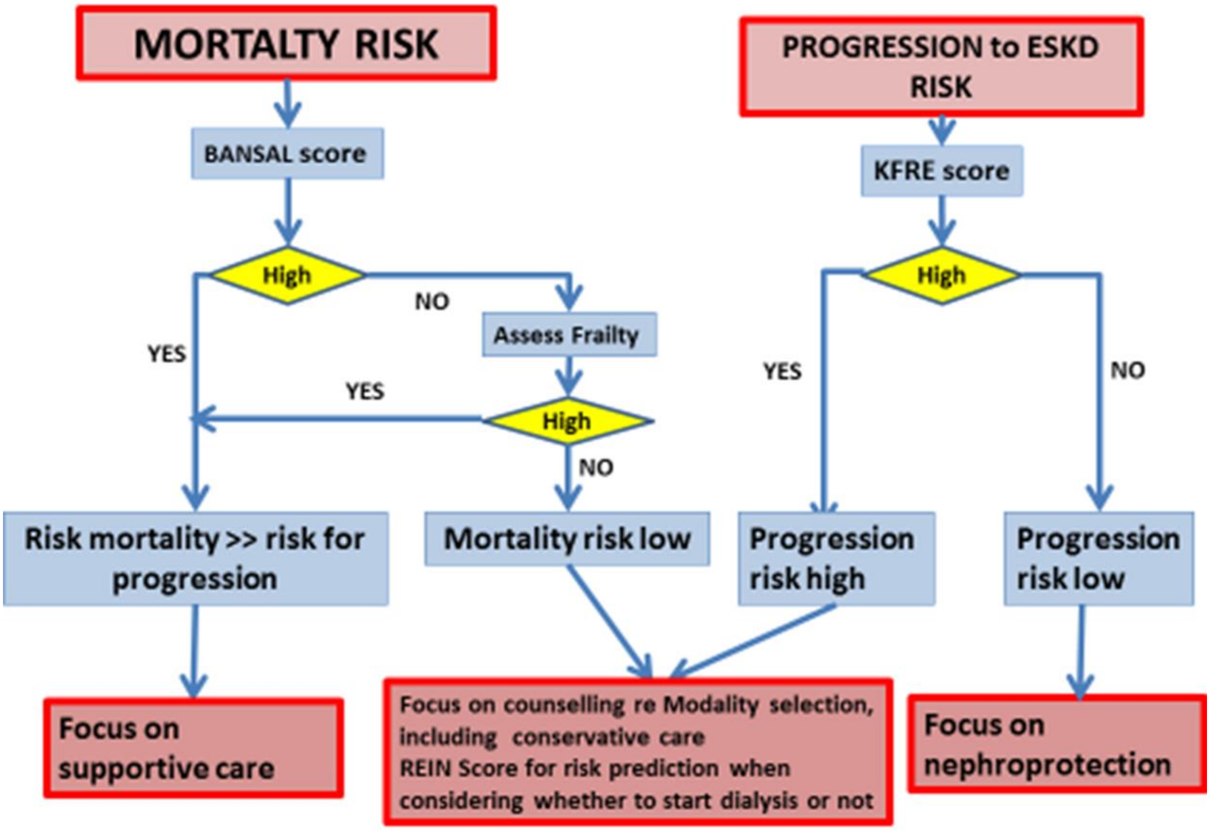

Figure 1. Decision flow chart to guide shared decision making when managing older patients with CKD of stage 3b or worse (eGFR <45 mL/min/1.73 m^2) based on estimation of mortality risk using Bansal score[14] and risk of progression to ESKD based on the score generated by the Kidney Failure Risk Equation (KFRE)[15]. For patients with eGFR <15 ml/min/1.73m^2, the REIN score[16] provides a risk prediction of death in the first 3 months after dialysis initiation.

The findings demonstrated good overall agreement between actual and predicted end-points for both equations. Of note, and maybe for some strikingly, only 42 of the 1188 patients (3.5%) actually progressed to end-stage kidney disease over the 5 year observation period. Based on the KFRE, this was predicted to be 4.9%. In stark contrast, mortality over the 5 year follow-up period was around 10-fold higher, with 462 patients (38.9%) dying versus a predicted mortality of 30.1% based on the Bansal equation. Both equations thus appeared well calibrated in this cohort, though some non-linearity of the observed vs predicted mortality slope implied some slight underestimation of mortality by the Bansal equation at lower risk levels. The ability to discriminate between patients progressing to ESRD and those not, was excellent (C-statistic 0.93), whilst the accuracy of death prediction was moderate (C-statistic 0.71).

Concurrent application of the prediction equations in the algorithm demonstrated that, whilst only 31 patients had a risk of progressing to ESKD over a 5 year period greater than their risk of death over the same period, the majority, 19 (61%) of these actually did progress to ESKD during that time, whilst five (16%) died during follow-up, and 7 (23%) experienced neither event. The important baseline characteristics which discriminated between progression to ESKD, death and event-free survival over the follow-up period included age, eGFR and health status. When these factors were examined in the study population, a number of findings emerged. In the very elderly (≥80 years), only two out of 598 patients (0.3%) progressed to ESKD in the next 5 years. Progression to ESKD was much less frequent than death at all levels of baseline eGFR, except <15 ml/min/1.73m^2, which is in keeping with the findings of previous studies[8,10]. Low levels of self-reported health at baseline were associated with death during follow-up, though a large proportion of patients who progressed to ESKD were also in this category.

While these findings provide welcome support for the potential utility of the ERBP-proposed algorithm in facilitating management of older patients with advanced kidney disease, some methodological issues should be considered. As in most registries, there is an assumption that the number progressing to ESKD is equivalent to the number actually starting on RRT. The underlying reason for this is that there is no specific definition for “ESKD” other than the start of RRT. As a consequence, there is no option to capture patients with CKD class 5 but not on dialysis. Most regional and national registries also lack the option to register this group of conservatively managed patients with ESKD. Hence it is not possible to identify the proportion of patients who would otherwise have started on RRT but may have opted for conservative management. Some of these would have died and others would still be alive but not receiving RRT. The authors acknowledge this limitation and quote Norwegian registry data which suggest that7-16% opt for conservative management. Another issue is the challenge of defining frailty. Using the data available in the HUNT study, only 7.2% of the study cohort were designated as frail, whereas published figures for a population at dialysis initiation, report up to 73%[19].

It is axiomatic that the ERBP algorithm does not define thresholds above which risk is designated as high, since thresholds will vary greatly between individuals according to their circumstances and preferences. Hallan et al[17] tackle this issue using Decision Curve Analysis[18] applied within the study cohort, to examine the clinical utility of the ERBP and other referral algorithms across a hypothetical range of patients' valuation of harm versus benefit. Benefit is defined as the timely referral for preparation for RRT in those who progress to ESKD as their first event, harm as the same referral in those who die as their first event, and utility (net benefit) for an individual is the benefit minus the harm for the total group, adjusted for the individual patient's perception of the trade-off between harm and benefit. Using this approach a number of algorithms were compared. The authors concluded that the ERBP algorithm[13], which the authors interpret as recommending referral when "ESKD risk > mortality risk provided the patient is not frail", is not the best at any level of patient valuation of harm versus benefit. The current KDIGO recommendation[20], to refer those whose 5 year ESKD risk > 50% (1 year risk >10%), was found to be appropriate only for those patients whose approach to referral was conservative i.e. those who considered the harm to benefit ratio as less than 1:1. For those with a more aggressive approach, referral was said to be beneficial if eGFR <25 ml/min/1.73m^2 provided they were under 80 years of age. On a more philosophical level, when looking at the Decision Curve Analysis, all algorithms taking into account the ratio of mortality vs progression risk, performed equally well in the "average" patient (i.e. in the preference range 2:3 to 3:2).

The interpretation of the authors that the ERBP algorithm recommends referral "ESKD risk > mortality risk provided the patient is not frail" is an oversimplification not fully consistent with the spirit of the guideline. In fact referral is recommended for all patients whose risk of ESKD is high provided that their mortality risk is not very much higher than their ESKD risk or they are frail, since for these latter patients management recommendations might focus on a supportive/palliative approach. Following the algorithm, interpreted in this way, many patients would be referred whose predicted mortality risk only moderately exceeds their ESKD risk. In these circumstances, the shared decision making process, which referral would trigger, would encompass both the option of preparation for RRT and the option of pursuing a conservative pathway. As mentioned Hallan et al could not take into account the conservative management option, as they lacked the data to do so.

The recommendation that referral may be beneficial for patients under 80 when their eGFR is <25 ml/min/1.75m^2, regardless of rate of progression, may also pose problems. As already alluded to, the rate of progression of CKD tends to be slow in older patients[7-10] and the mortality rate high[10]. The authors have themselves demonstrated that very few patients with this level of renal function progress to ESKD, so most patients would be referred inappropriately. Preparation for ESKD in these patients would entail fistula formation, though the proportion of unnecessary procedures in older patients with this level of renal function has been shown to be high[21]. In these circumstances referral without reference to the trajectory of renal functional decline would seem inappropriate[22,23].

The discussion above highlights the complexity of the decision making pathway in older patients with advanced CKD. The core purpose of this pathway is to integrate patient preferences with an honest appraisal of the available evidence relating to viable treatment options, in a process of shared decision making. Hallan et al have provided evidence that the two equations deployed in the ERBP algorithm are fit for purpose in this context. They also clearly illustrate the impact of patient preference on decision making. Other approaches may emerge, for instance Grams et al[24] have produced a risk prediction tool for patients with GFR<30ml/min/1.73m^2 that takes account of competing risks, the outputs of which include 2 and 4 year probabilities of the requirement for renal replacement therapy, non-fatal cardiovascular events, and death. Other models have emphasized the predictive utility of the surprise question[25] and impaired nutritional status[26] in this setting. We need to know much more about how to gain an understanding of an individual's perception of, and response to, risk[27], and how best to communicate risk in conversations with patients[28]. These are crucial issues and central to effective shared decision-making which is at the core of the ERBP algorithm.

Conflict of Interest. None of the authors have any conflict of interest with respect to this article

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