A DECISION-MAKING ALGORITHM PROPOSAL FOR PICCS AND MIDLINES INSERTION IN PATIENTS WITH ADVANCED KIDNEY DISEASE. A PILOT STUDY.

Arianna Bartoli[1], Maurizio Gallieni[1,2], Chiara Cogliati[1], Francesco Casella[1], Maria Calloni[1], Chiara Melchionda[1], Marco Heidempergher[2], Antonella Foschi[4], Antonio Luca Brucato[1], Giulia Rizzi[1], Massimiliano Quici[1], Antonio Gidaro[1]

1. Department of Biomedical and Clinical Sciences “Luigi Sacco”, University of Milan, Luigi Sacco Hospital Milan Italy
2. Nephrology and Dialysis Unit, ASST Fatebenefratelli Sacco, 20131 Milan, Italy.
3. Department of Infectious Diseases, Luigi Sacco Hospital, Milan, Italy

Corresponding Author: Gidaro Antonio ORCID number: 0000-0002-5379-1091

Antonio Gidaro, MD,

Tel+39 3401595182

Mail: gidaro.antonio@asst-fbf-sacco.it

Address: Via G. B. Grassi N° 74 H. Sacco Milan 20157

Ethics statement: All the data were anonymized. The Institutional Review Board of our University Hospital (Luigi Sacco Hospital, University of Milan, Italy) approved the study protocol (“BUCAVIP”; July 7, 2021). The study was carried out in compliance with the ethical principles of the Declaration of Helsinki (with amendments) and Good Clinical Practice.

Funding: none.

Conflict of interest: The authors have no conflicts of interest to disclose as described by the Journal of Nephrology.

Informed consent: the patients gave his informed consent prior to his inclusion in the study.

Acknowledgement: thank you to Dr. Mauro Pittiruti for the valuable advices.

ABSTRACT

Introduction: Kidney Disease Outcomes Quality Initiative clinical practice guidelines recommends avoiding placement of peripherally inserted vascular access devices in patients on dialysis or grade III B chronic kidney disease (CKD). On the other hand, many patients with severe CKD have poor prognosis.

The aim of this study is to carry out a global assessment of mortality at 2 years through Charlson Comorbidity Index (CCI) and Beclap score in patients with PICCs or Midlines, assuming that in those with estimated high mortality rate at two years, it could be acceptable to implant a PVAD if necessary.

Methods: we analyzed data on patients with PICCs or Midlines inserted from October 2018 to November 2019. CCI, Beclap score and Estimated Glomerular Filtration Rate (eGFR) were calculated for each patient at the time of the catheter insertion. We then followed patients for two years to assess two-year mortality for each.

Results: 131 patients were enrolled. The people with eGFR<45ml/min/1.73m2 were 49(37,4%). 2-years mortality rate was 57,3%. The cut off derived from ROC curve analysis of 15 for Beclap score and 5 for CCI, showed good sensitivity and specificity in predicting mortality of the total population, patients without an oncological disease and patients with eGFR<45ml/min/1.73m2.

Conclusion: CCI and Beclap score are good predictors of 2 years mortality. Nephrologists, physicians and nurses can use these tools before implantation of the vascular access in the evaluation of patients at risk for future dialysis, instead of relying exclusively on renal function to decide whether implanting PICCs or Midlines.

Keywords: Chronic kidney disease (CKD); Peripherally inserted central catheters (PICCs); Midlines catheters; Charlson Comorbidity Index (CCI); Beclap score; mortality

INTRODUCTION

Peripherally inserted central catheters (PICCs) and Midlines catheters are widely used in everyday clinical practice [1]. Unfortunately, their use could be associated with complications such as stenosis, thrombosis and obliteration of the central and peripheral veins in which they dwell [1]. These complications are of particular interest in patients with chronic kidney disease (CKD) as they may compromise the longevity of a future possible dialysis [2].

For these reasons the 2019 update of the Kidney Disease Outcomes Quality Initiative (KDOQI) clinical practice guidelines recommends the preservation of central and peripheral upper extremity veins from vascular damage by avoiding the placement of Peripheral Vascular Access Devices (PVAD) or PICCs in the arm or forearm in patients on dialysis or grade III B CKD [3].

However, a review of the literature shows that the use of vascular catheters in patients with renal failure, especially in an intensive care unit (ICU) setting, is common in clinical practice and discordant with guidelines [2][4].

On the other hand, the above-mentioned guidelines allow the placement of a vascular catheter in a patient with a life expectancy of less than two years. This is because even if the patient under consideration were to undergo dialysis, he would only be there for a short time [3].

Many patients with severe CKD have poor prognosis. Othman et al reported an overall death rate for the year post PICC insertion of 38.7%. Because of this high mortality in the year after catheter insertion, only 8,1% of the patients with III B CKD or lower begin dialysis in the year post catheter insertion [2].

The Kidney Disease Improving Global Outcome [3] and the International Society of Nephrology [5] recommendations also highlight the interest of using prognostic scores to predict death or start of renal replacement therapy for shared medical

decisions; the scores suggested are the GRAMS [6] and BANSAL [7] scores. Moreover, a recent review by Prouvot et al [8] found other four equations (SCHMIDT [9]; WEISS [10]; GOLDFARB [11]; LANDRAY [12]) predicting death before dialysis in CKD patients.

Unfortunately, none of these scores could be used in our study because they were only tested in a specific age or eGFR group or because they included laboratory parameters that are not routinely requested.

Many other mortality risk score are reported in the literature, the most used is Charlson Comorbidity Index (CCI) [13] that calculate the estimated mortality risk at ten and two years; a newer and promising score is Beclap score [14] that assess mortality of non-oncological patients at three and six months.

These simple tools could add a more evidence-based and individualized approach for vascular access management in patients with CKD providing a prognostic evaluation in order to perform a risks and benefits assessment, assuming that in patients with estimated high mortality rate at two years it could be acceptable to implant a vascular access if necessary.

Thus, the aim of this study is to carry out a global assessment of mortality at 2 years through Charlson Comorbidity Index (CCI) [13] and Beclap score [14], in order to identify patients with poor survival prognosis, assuming they would not need chronic hemodialysis. We than verified that the follow up of these patients confirmed death within two years and no dialysis.

METHODS

In this prospective observational study, we analyzed data on patients with PICCs or Midlines inserted from October 2018 to November 2019 in internal medicine wards at L. Sacco Hospital Milan. All catheters were implanted by the local PICC-team

composed of trained physicians or nurses. The devices have been positioned following the protocol “Safe insertion of PICCs (SIP)” [15]. Written informed consent to vascular procedure and study participation was obtained for all study participants.

Eligible subjects were inpatients that required a PICC or a Midline catheter because of a difficult intravenous access (DIVA) or an expected need of intravenous therapy longer than 6 days. These were patients judged clinically suitable for catheter insertion. Exclusion criteria included stay in the Intensive Care Unit or ongoing dialysis.

Charlson Comorbidity Index [13], Beclap score [14] and renal function were calculated for each patient at the time of the catheter insertion in order to estimate patients’ prognosis and to evaluate the eventual presence of CKD at enrollment time.

We then followed patients for two years through the SISS regional network system (Sistema Informativo Socio Sanitario) in order to assess patients’ two-year mortality. In this way, the estimated prognosis calculated at the time of implantation could be compared with the effective mortality rate recorded at two years.

A subgroup analysis was then performed taking into account patients with eGFR < 45 ml/min/1.73m2 and without an oncological disease.

The study protocol complied with the Declaration of Helsinki and the Institutional Review Board of our University Hospital (Luigi Sacco Hospital, University of Milan, Italy) approved the study protocol (“BUCAVIP”; July 7, 2021).

Data were expressed as mean ± standard deviation (normally distributed data), median and interquartile range (non-normally distributed data) or as absolute frequency and percentage (binary or ordinal data), as appropriate. Chi square or Fisher exact tests were used in the group's comparison. Student T-test was used for comparison between groups. P-value less than 0.05 was considered statistically significant. A ROC curve analysis was performed to identify the cut offs to be used

as decision values. The cutoff chosen by ROC analysis was evaluated with a Kaplan-Meier curve.

The statistical analysis of data was done by using Excel (Office program 2016) and SPSS (statistical package for social science-SPSS, Inc., Chicago, IL version 20).

RESULTS

A total of 131 patients were enrolled; the median age was 71,8 ± 15,4, 64 (48,9%) were males. The catheters implanted were 99 Midlines (75,5%) and 32 PICCs (24,5%).

Patients with an eGFR < 45 ml/min/1.73/m^2 were 49 (37,4%), no one of the CKD patients required dialysis during the two years of follow-up. Only a woman began strict follow-up in a pre-uremic outpatient's clinic.

Two-years mortality rate was 57,3% (13,7% during the hospital stay, 43,5% after it). Charlson Comorbidity Index and Beclap score were on average respectively 5,98 ± 3,12 and 19,68 ± 20,74 (Table 1).

In the subgroup analysis, patients without oncological disease and those with eGFR < 45 mL/min/1.73 m2 were considered (respectively 94 and 49 patients). In this subgroup analysis, comparing the subgroup with reduced renal function to general population, there were a significant lower albumin 's levels, a worst estimated prognosis with both CCI and Beclap score (CCI 5,98 ± 3,12 in total population versus 6,92 ± 2,28 in patients with low eGFR with p-value 0,029; Beclap score 19,68 ± 20,74 in total population versus 33,37 ± 23,77 in reduced eGFR subgroup with p-value < 0,01). At two-year follow-up patients with eGFR<45 mL/min/1.73 m2 at baseline showed a significantly higher mortality compared to the general population (57,3% in total population versus 75,51% in the subgroup with p-value 0,024). (Table 1)

As expected, a statistical significance better prognosis was estimated with CCI for non-oncological patients compared to the general population (CCI 5,98 ± 3,12 in total population versus 5,24 ± 2,89 in no oncological disease subgroup, p-value 0,036). At two-year follow-up no difference in mortality rate was assessed comparing the whole population with non-oncological subgroup (57,3% in total population versus 53,19% in the subgroup with p-value 0,54).

Figure1 shows the ROC curve for CCI and Beclap scores in the whole population. Figure 2a shows the ROC curve for patients without an oncological disease. Figure 2b shows the ROC curve for patients with eGFR < 45 ml/min/1.73 m2.

Beclap and Charlson scores cut-off derived from ROC curves showed good sensitivity (SE) and specificity (SP) in predicting the two-years mortality of the total population: in particular, a cut-off of 5 for CCI showed a sensitivity of 0,855 and a specificity of 0,717, while a cut-off of 15 for Beclap Score showed a sensitivity of 0,652 and a specificity of 0,917 (Figure 1).

Similar results were found in the subgroup of patients with an eGFR less than 45 ml/min/1.73 m2 (CCI: SE 0,902, SP 0,647; for Beclap Score SE 0,756, SP 0,824) (Figure 2a) and without oncological disease (for CCI: SE 0,795, SP 0,74; for Beclap Score SE 0,636, SP 0,92) (Figure 2b).

DISCUSSION

To the best of our knowledge, this study is the first to evaluate the parameter of estimated prognosis in patients with CKD and inserted peripheral vascular access, assuming that in patients with a high mortality risk at two years, it could be acceptable to implant a vascular access if necessary.

A review of the literature shows that the use of vascular catheters in patients with renal failure is common in clinical practice and discordant with guidelines.

Paje et al., in a big prospective cohort study of 20545 patients, found that approximately 1 of 4 PICCs (23,1%) was inserted in a patient with eGFR < 45 ml/min/1.73m2; the median age of the population studied was 65,1 years [4]. Similarly, Othman et al. [2] showed a proportion of 26,7% of patients with vascular access and stage III B or more advanced CKD. In our study the percentage of patients with severe CKD was 37,4%.

The rate of patients with vascular access and eGFR < 45 ml/min/1.73m2 in our population is higher than in the literature. A possible explanation could be, the higher average age in our study (71,8 years) compared to the studies mentioned (65,1 years). This makes the number of patients with CKD higher and the estimated prognosis worse.

Nevertheless, no patient required dialysis, this could be due to the small cohort examined, combined with the low incidence of developing end-stage renal disease reported by the literature. In fact, Turin et al, in a Canadian cohort of patients with eGFR 30–44 ml/min/1.73m2, reported a percentage of 0.8% for years of people developing CKD requiring dialysis [16].

Algorithms presented in the literature leave up to the assessment of the doctor, in accordance with the guidelines, to decide on the implantation, considering the placement of a vascular catheter in a patient with a life expectancy of less than two years to be acceptable. [17] Moreover, this strategy was also adopted during our enlistment. Nevertheless, assessing mortality is a difficult matter even for experienced physicians and is often affected by subjective bias, so results may change depending on the evaluator. Based on this issue, it is fundamental to find an objective instrument that could help clinicians to solve this problem.

The scores used in our study provide a simple tool that can be easily implemented and quickly interpreted by nurses or staff without specific knowledge. Such scores

have also been shown to accurately predict short-term mortality: in the general population, the odds ratio for CCI greater than 5 was 17,4 (CI: 6,5-46,6), and for Beclap score greater than 15 was 42,9 (CI: 13,3-138.3). This demonstrates the validity of these scores and the chosen cut-offs. Moreover, the combined use of the two scores balances the weakness of single tool: CCI's cut off has high SE and low SPE, Beclap score is specular with high SPE and low SE.

Although this is a small observational study with a limited number of patients and further research is needed to make this evidence stronger, considering the data collected we propose a new decision algorithm for vascular access insertion in patients with CKD.

In particular, our new algorithm suggests the insertion of PICCs or Midline catheters in cases of eGFR > 45 ml/min/1.73m2 or in cases of eGFR < 45 ml/min/1.73m2 but high probability of death at two years (Beclap score > 15 points, CCI > 5 points). Catheter insertion is not recommended in patients with advanced CKD stage III B or more but with a good chance of survival at two years and therefore a high probability of dialysis, in order to preserve vascular access for possible future dialysis. (Figure 3). In patients with Beclap score < 15 and CCI > 5 or with Beclap score > 15 and CCI < 5 a case-by-case evaluation of the specialist is necessary. CCI and Beclap score discordance occurred in 29.8% of the total study population and 20.4% of patients with eGFR < 45 ml/min. Using the proposed algorithm, only about one in five cases would then need the specialist's case-by-case evaluation.

Certainly, in those patients in whom it is decided to implant a PICC or a Midline after applying the score, it is good practice to apply all precautions to minimize the risk of complications. For example, it is known that limiting the catheter’s diameter may reduce the risk of PICC or Midline related venous thrombosis. [2,18,19]

We note some limitations of our findings. First, this report includes a limited number of patients; furthermore, this is a single-center study enrolling patients admitted to an internal medicine department; finally, Beclap score has been validated by only one study. For these reasons our results require confirmation in larger multicenter studies.

CONCLUSION

In conclusion, we can affirm that CCI and Beclap score are good predictors of 2 years mortality in patients with PICC or Midline catheters.

Nephrologists, physicians and nurses can use these tools before insertion of the catheters in the evaluation of patients at risk for future dialysis, instead of relying exclusively on renal function to decide whether implanting peripheral venous accesses.

Indeed, in many cases the need for reliable vascular access for infusion of drugs such as antibiotics, hydration or diuretics is crucial for the patient and can significantly change the subject's quality of life.

Furthermore, this tool could be useful to identify the frailest patients that could benefit more from a nephrological consultation focused on improving their prognosis and not only to allow vascular access implantation.

BIBLIOGRAPHY

[1] McGill RL, Ruthazer R, K. B. Meyer KB et al. Peripherally inserted central catheters and hemodialysis outcomes. *Clin J Am Soc Nephrol* 2016; 11:1434-1440

[2] Othman K, Abdulrahman S, Salman R et al. Peripheral central catheter insertion in low eGFR patients: Retrospective single institution study. *J Vasc Access* 2021; 1-4

[3] Lok CE, Huber TS, Lee T et al. KDOQI Vascular Access Guideline Work Group. KDOQI clinical practice guideline for vascular access: 2019 update. *Am J Kidney Dis* 2019; 75(4)(suppl 2): S1-S164

[4] Paje D, Rogers M, Conlon A, et al. Use of peripherally inserted central catheters in patients with advanced chronic kidney disease. A prospective cohort study. *Ann Intern Med* 2019; 171:10-18
[5] Pena MJ, Stenvinkel P, Kretzler M et al. Strategies to improve monitoring disease progression, assessing cardiovascular risk, and defining prognostic biomarkers in chronic kidney disease. *Kidney Int Suppl* 2017; 7:107–113
[6] Grams ME, Sang Y, Ballew SH et al. Predicting timing of clinical outcomes in patients with chronic kidney disease and severely decreased glomerular filtration rate. *Kidney Int* 2018; 93:1442–1451
[7] Bansal N, Katz R, De Boer IH et al. Development and validation of a model to predict 5-year risk of death without ESRD among older adults with CKD. *Clin J Am Soc Nephrol CJASN* 2015; 10:363–371
[8] Prouvo J, Pambrun E, Antoine V, Couchoud C, Vigneau C, Roche S, Francois M, Mariat C, Babici D, Prelipcean C, Moranne O; Low performance of prognostic tools for predicting death before dialysis in older patients with advanced CKD. *J Nephrol* 2021; 1-9
[9] Schmidt RJ, Landry DL, Cohen L et al. Derivation and validation of a prognostic model to predict mortality in patients with advanced chronic kidney disease. *Nephrol Dial Transplant* 2018; 15: 1951-1962
[10] Weiss JW, Platt RW, Thorp ML et al. Predicting mortality in older adults with kidney disease: a pragmatic prediction model. *J Am Geriatr Soc* 2015; 63:508–515
[11] Goldfarb-Rumyantzev AS, Gautam S, Dong N, Brown RS Prediction model and risk stratification tool for survival in patients With CKD. *Kidney Int Rep* 2018; 3:417–425
[12] Landray MJ, Emberson JR, Blackwell L et al. Prediction of ESRD and death among people with CKD: the chronic renal impairment in Birmingham (CRIB) prospective cohort study. *Am J Kidney Dis* 2018; 56:1082–1094
[13] Charlson ME, Pompei P, Ales KL, MacKenzie CR; A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; 40(5):373-83
[14] Brucato A, Ferrari A, Tiraboschi M et al. Three-month mortality in permanently bedridden medical non-oncologic patients. The BECLAP study (permanently BEdridden, creatinine CLearance, albumin, previous hospital admissions study). *Eur J Intern Med* 2020; 72:60-66
[15] Brescia F, Pittiruti M, Spencer TR et al. The SIP protocol update: Eight strategies, incorporating Rapid Peripheral Vein Assessment (RaPeVA), to minimize complications associated with peripherally inserted central catheter insertion. *J Vasc Access;* 2022; 1-9
[16] Turin, Tanvir Chowdhury et al. Lifetime risk of ESRD. *Journal of the American Society of Nephrology JASN* 2012; 23: 1569-78
[17] Oza-Gajera B, Davis J, Farrington C et al. PICC line management among patients with chronic kidney disease. *J Vasc Access* 2021; 1-9
[18] Chopra V, Kaatz S, Conlon A, et al. The Michigan Risk Score to predict peripherally inserted central catheter-associated thrombosis. *J Thromb Haemost* 2017; 15: 1951–1962

[19] Ratz D, Hofer T, Flanders SA, et al. Limiting the number of lumens in peripherally inserted central catheters to improve outcomes and reduce cost: a simulation study. *Infect Control Hosp Epidemiol* 2016; 37: 811–817

Table 1 - Characteristics of patients at baseline and at follow-up in total population, in the subgroup of patients without an oncological disease and in patients with eGFR < 45 ml/min/1.73m2.

Figure 1 - ROC and Kaplan Meier curves evaluating mortality scores in total population.
The left picture (ROC curves) shows three lines:

- the dotted line shows the CCI values
- the dash-dotted line shows the Beclap score values
- the solid line shows the reference line

The middle picture shows Kaplan Meier curves for CCI score:

- the dotted line represents mortality of patients with CCI more than 5 or equal
- the solid line represents mortality of patients with CCI less than 5

The right picture represents Kaplan Meier curves for Beclap score:

- the dotted line represents mortality of patients with Beclap more than 15 or equal
- the solid line represents mortality of patients with Beclap less than 15

The table under the pictures shows the details of the ROC area under the curve: standard error; lower and Upper limit; the chosen cut off with specificity and sensitivity; odds ratio with CI for patients with positive test.

Figure 2a - ROC and Kaplan Meier curves evaluating mortality scores in patients without an oncological disease. The left picture (ROC curves) shows three lines:

- the dotted line shows the CCI values
- the dash-dotted line shows the Beclap score values
- the solid line shows the reference line

The middle picture shows Kaplan Meier curves for CCI score:

- the dotted line represents mortality of patients with CCI more than 5 or equal
- the solid line represents mortality of patients with CCI less than 5

The right picture represents Kaplan Meier curves for Beclap score:

- the dotted line represents mortality of patients with Beclap more than 15 or equal
- the solid line represents mortality of patients with Beclap less than 15

The table under the pictures shows the details of the ROC area under the curve: standard error; lower and Upper limit; the chosen cut off with specificity and sensitivity; odds ratio with CI for patients with positive test.

Figure 2b - ROC and Kaplan Meier curves evaluates patients with eGFR < 45 m/min/1.73 m2. The left picture (ROC curves) shows three lines:

- the dotted line shows the CCI values
- the dash-dotted line shows the Beclap score values
- the solid line shows the reference line

The middle picture shows Kaplan Meier curves for CCI score:

- the dotted line represents mortality of patients with CCI more than 5 or equal
- the solid line represents mortality of patients with CCI less than 5

The right picture represents Kaplan Meier curves for Beclap score:

- the dotted line represents mortality of patients with Beclap more than 15 or equal
- the solid line represents mortality of patients with Beclap less than 15

The table under the pictures shows the details of the ROC area under the curve: standard error; lower and Upper limit; the chosen cut off with specificity and sensitivity; odds ratio with CI for patients with positive test.

Figure 3 –The proposed algorithm tries to determine the possibility to place a vascular access line given the patient's renal function, Beclap score and CCI.

The first step is evaluation of the eGFR: if the eGFR is over 45ml/min/1.73m2, implantation is allowed.

If the eGFR is lower than 45ml/min/1.73m2, we need to assess CCI and Beclap score.