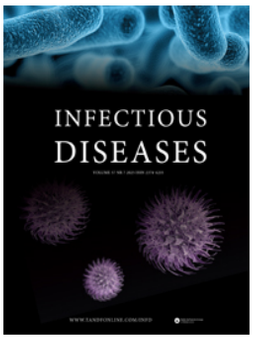

Infectious Diseases

ISSN: 2374-4235 (Print) 2374-4243 (Online) Journal homepage: www.tandfonline.com/journals/infd20

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To cite this article: Sandra De la Rosa-Riestra, Belén Gutiérrez-Gutiérrez, Inmaculada López-Hernández, María Teresa Pérez-Rodríguez, Josune Goikoetxea Agirre, Antonio Plata, Eva León, María Carmen Fariñas Álvarez, Isabel Fernández-Natal, Jonathan Fernández-Suárez, Lucía Boix-Palop, Jordi Cuquet Pedragosa, Alfredo Jover-Sáenz, Juan Manuel Sánchez Calvo, Andrés Martín-Aspas, Clara Natera-Kindelán, Alfonso Del Arco-Jiménez, Pedro María Martínez Pérez-Crespo, Luis Eduardo López-Cortés & Jesús Rodríguez-BañoOn behalf of the PROBAC/GEIRAS-SEIMC/SAMICEI (09 Jul 2025): External validation of the predictive ability of Charson, SOFA, Pitt, INCREMENT-ESBL and bloodstream infection mortality Risk for 30-day-mortality in bacteraemia using the PROBAC cohort data, Infectious Diseases, DOI: 10.1080/23744235.2025.2527681

To link to this article: https://doi.org/10.1080/23744235.2025.2527681

INFECTIOUS DISEASES
https://doi.org/10.1080/23744235.2025.2527681

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RESEARCH ARTICLE

External validation of the predictive ability of Charson, SOFA, Pitt, INCREMENT-ESBL and bloodstream infection mortality Risk for 30-day-mortality in bacteraemia using the PROBAC cohort data

Sandra De la Rosa-Riestra[a,b], Belén Gutiérrez-Gutiérrez[a,b], Inmaculada López-Hernández[a,b], María Teresa Pérez-Rodríguez[c,d], Josune Goikoetxea Agirre[e], Antonio Plata[f], Eva León[g], María Carmen Fariñas Álvarez[b,h], Isabel Fernández-Natal[i], Jonathan Fernández-Suárez[j], Lucía Boix-Palop[k], Jordi Cuquet Pedragosa[l], Alfredo Jover-Sáenz[m], Juan Manuel Sánchez Calvo[n], Andrés Martín-Aspas[o], Clara Natera-Kindelán[p], Alfonso Del Arco-Jiménez[q], Pedro María Martínez Pérez-Crespo[g], Luis Eduardo López-Cortés[a,b] and Jesús Rodríguez-Baño[a,b]; On behalf of the PROBAC/GEIRAS-SEIMC/SAMICEI

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ABSTRACT

Introduction: The development of predictive mortality scores for bacteraemia is fundamental for identifying patients in whom increasing our management efforts. However, it is necessary to assess the validity of the results obtained when they are applied to new cohorts.

Methods: We evaluated the ability of different scales (Charlson, also age-adjusted Charlson and updated Charlson, SOFA, Pitt, INCREMENT-ESBL and BSIMRS) to predict 30-day mortality in bacteraemia through the AUROC and calibration plots. The scales were applied to specific patient from PROBAC cohort (prospective, multicentre with bacteraemia of any aetiology) according to the population in which the scale was originally developed. We also applied the recently developed PROBAC score (this time applied to the entire PROBAC cohort, rather than only to patients who did not die within 48 h of blood culture collection as in the original development of the scale).

Results: After applying Charlson, age-adjusted Charlson, updated Charlson, SOFA, Pitt and PROBAC to the entire PROBAC cohort, we obtained AUROC values: 0.60 (95% CI: 0.58–0.62); 0.62 (95% CI: 0.60–0.64); 0.60 (95% CI: 0.58–0.62); 0.69 (95% CI: 0.66–0.71); 0.71 (95% CI: 0.69–0.82) and 0.80 (95% CI: 0.79–0.81), respectively. INCREMENT-ESBL was applied only to gram negative bacteraemia yielding 0.81 (95% CI: 0.79–0.82) and BSIMRS to gram negative bacteraemia who received adequate empirical antibiotic yielding 0.72 (95% CI: 0.70–0.75).

ARTICLE HISTORY
Received 22 March 2025
Revised 21 June 2025
Accepted 25 June 2025

KEYWORDS
Bloodstream infection; mortality; prognostic factors, adult, Spain, logistic models

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/23744235.2025.2527681.

Conclusions: Scores that have been developed in bacteraemia cohorts and have been used for the prediction of short-term mortality were found to be better at predicting mortality in our analysis.

Introduction

Bacteraemia, either community- or hospital-acquired, is a leading cause of mortality in hospital admitted patients, with mortality rates ranging 13%–17% [1,2]. However, the mortality risk is heterogeneous according to patients' features, severity of infection, aetiology and source. Predicting mortality in patients with bacteraemia according to specific variables can be useful to improve patient classification for better management. They are also useful for stratification of patients in clinical researchto control baseline risks when comparing therapeutic interventions.

Several scores are widely used to predict mortality in patients with bacteraemia. However, changes in population epidemiology (e.g. changes in aetiologies or predominance of specific patient groups) or in some aspects of clinical management (e.g. better and earlier diagnosis, earlier or more effective treatments) may affect the predictive ability of any score, which should therefore be retested in different periods of time and populations. While performance of predictive scores may seem adequate in the derivation dataset, external validation in external cohorts in which they are intended to be used is needed to understand their generalisability.

The objective of this research was to validate some of the most frequently used scores, including the Charlson, SOFA, Pitt, INCREMENT-ESBL and Bloodstream Infection Mortality Risk score (BSIMRS) in their predictive capacity for 30-day mortality in patients with bacteraemia using the PROBAC cohort.

Materials and methods

Design, participants and variables

This analysis was performed using the data from the PROBAC project, a prospective, multicentre, observational cohort study which included consecutive episodes of bacteraemia in patients older than 14 years diagnosed between October 2016 and March 2017 in 26 Spanish hospitals. The methodology of this study was previously detailed [3,4]. In summary, bacteraemia episodes were included if the patients were admitted to the hospital and associated with signs and symptoms of infection; potential contaminants such as coagulase-negative staphylococciwere included only if isolated from more than one blood drawn. New episodes in the same patient were only included if occurring after 3 months of the previous one. Patients were followed for 30 days. Day 0 was defined as the day of blood culture collection. The main endpoint was 30-day all-cause mortality.Inappropriate empirical therapy was referred to the first 24 h after blood cultures were obtained and according to *in vitro* sensitivity.For each patient we collected this data corresponding to the worst value that occurred during the first 24 h. Consequently, the scores were applied during the very first 24 h.

Data were collected by trained investigators at each site and included demographics, underlying conditions, McCabe classification, Charlson comorbidity index, Pitt score, SOFA score, source of infection, microbiological data and antimicrobial treatment.

The PROBAC project was approved by the Ethics Committee of the Hospital Universitario Virgen Macarena (reference code: FIS-AMO-2016-01) and those of the participating centres. Due to the observational nature of the study, informed consent was not required. The project was registered on ClinicalTrials.gov (NCT03148769).

Mortality prediction scores

The scores studied for their validation in this analysis included the Charlson comorbidity score [5] (including also the age-adjusted [6] and updated Charlson [7] variants), the Pitt score [8], the Sequential Organ Failure Assessment (SOFA) score [9], the INCREMENT-ESBL score [10] and the Bloodstream Infection Mortality Risk (BSIMRS) score [11]; in addition, the score previously developed with this cohort

(the PROBAC score [3]), was also used as a reference. The features of the scores and the conditions for their application to the PROBAC cohort are specified in Table 1. The variables included in each score are shown in Supplementary Tables S1–S6.

Statistical analysis

Continuous variables were expressed as median and interquartile range, and categorical variables as absolute number and percentages. The different scores were applied to either all patients in the PROBAC cohort or specific subpopulations, as specified in Table 2, according to the populations in which the scores were originally developed. For each of the scores, the discrimination ability for observed 30-day mortality was assessed by calculating the area under the receiver operating characteristic curve (AUROC); calibration plots were developed and visually examined. Analyses were performed with IBM Statistics for Windows, version 25.0 (IBM Corp, Armonk, NY, USA).

Results

Overall, the complete PROBAC cohort included 6313 patients; the full set of patients was used to test the Charlson, Pitt and SOFA scores. Median age was 71 years, 3623 (58.5%) were male, and the most frequent comorbidities were cancer (1648, 26.1%) and diabetes mellitus (1518, 24%). *Escherichia coli* (2702, 42.8%), *Staphylococcus aureus* (557, 8.8%) and *Klebsiella pneumoniae* (545, 7.2%) were the most frequent aetiologies. The predominant identified sources of infection were the urinary tract (2039, 32.3%), the biliary tract (850, 13.5%) and vascular catheter-related (769, 12.2%); 30-day mortality was 14.8% (933 patients). Table 3 describes the demographic, clinical and microbiological characteristics of patients.

The median Charlson comorbidity index scale was 2 (IQR, 0-3; range 0–15). The AUROC for observed 30-day mortality was 0.60 (95% CI: 0.58–0.62) (Supplementary Figure S2). Mortality was 10% among patients with a score of 0 point, 10%–20% for scores between 1 and 4 points, and $>$20% for scores $\geq$5.

Table 1. Features of the mortality-predictive scores evaluated.

Score (year of derivation)	Variables included	Population in derivation cohort	Outcome
Charlson comorbidity index (1984) (4)	Miocardial infarction, heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, peptic ulcer, liver disease, diabetes mellitus, hemiplegia, chronic kidney disease, haematologic cancer, solid cancer, AIDS/HIV	Patients admitted to the hospital	1-year mortality
Age-adjusted Charlson comorbidity index (1982–1985) (5)	As above plus age	Patients admitted to the hospital	1-year mortality
Updated Charlson comorbidity index (2004) (6)	Heart failure, dementia, chronic pulmonary disease, connective tissue disease, liver disease, diabetes mellitus, hemiplegia, chronic kidney disease, solid cancer, AIDS/HIV	Patients admitted to the hospital	1-year mortality
Pitt (1982–1986) (7)	Temperature, hypotension, mechanical ventilation, heart failure, mental status	Patients with Pseudomonas aeruginosa bacteremias	10-day mortality
SOFA (1995) (8)	Respiratory parameters, Glasgow scale, blood pressure and amines need, and bilirubin, creatinine level, and platelets count	Septic patients included in the European /North American Study of Severity Systems.	Degree of organ dysfunction
PROBAC (2016–2017) (2)	Age, McCabe classification, cancer, liver disease, aetiology, source, polymicrobial, recent use of antimicrobials, mental status, blood pressure, respiratory parameter	Patients with bacteraemia; dead in first 48 hours excluded	30-day mortality
INCREMENT-ESBL (2004–2013) (9)	Age, *Klebsiella*spp, source other than UCI, McCabe classification, Pitt, sepsis, inappropriate early treatment	Patients with bacteraemia due to ESBL-producing Enterobacterales	30-day mortality
Bloodstream infection mortality risk score (2001–2006) (10)	Cancer, liver disease, source other than urinary or catheter, Pitt	Patients with bacteraemia due to gram negative bacteria receiving active empirical therapy	28-day mortality

Table 2. Summary of median (interquartile range) values and areas under the operating receiving curves for observed data of the different scores applied to different subpopulations of the PROBAC cohort.

Score	Population studied in PROBAC cohort	Median value (IQR), survivors	Median value (IQR), dead patients	AUROC (95% CI)
Charlson index	All patients	2 (0–3)	2 (1–4)	0.60 (0.58–0.62)
Age-adjusted Charlson index	All patients	4 (2–6)	6 (4–8)	0.62 (0.60–0.64)
Updated Charlson index	All patients	2 (0–4)	3 (1–6)	0.60 (0.58–0.62)
SOFA score	All patients	2 (1–5)	5 (3-8)	0.69 (0.66–0.71)
Pitt score	All patients	1 (0–2)	3 (1–6)	0.71 (0.69–0.82)
PROBAC score	All patients	3 (2-6)	8 (6–11)	0.80 (0.79–0.81)
INCREMENT-ESBL score	Bacteraemia due to Gram negative organism	7 (5–10)	11 (9–14)	0.81 (0.79–0.82)
BSI-MRS score	Bacteraemia due to Gram negative organism and active empirical therapy	4 (0–6)	7 (4–9)	0.72 (0.70–0.75)

IQR: interquartile range.

When applying the age-adjusted Charlson scale, the median score was 4 (IQR, 3–6, range 0–19); the AUROC for observed mortality was 0.62 (95% CI: 0.60–0.64) (Supplementary Figure S3). We observed 10% mortality for 0 points, 10%–13% for 1 to 4 points and 17% for $\geq$5 points. The median value of the updated Charlson scale was 2 (IQR, 0–3; range 0–14) and the AUROC for observed mortality was 0.60 (95% CI: 0.58–0.62) (Supplementary Figure S4). We observed a 12% mortality for 0 points, 12%–25% for 1–3 points, and 25% for $\geq$4 points.

The median SOFA score was 2 (IQR, 0–4; range, 0 and 22), meaning that 50% of patients had criteria for sepsis. The AUROC for observed mortality was 0.69 (95% CI: 0.66–0.71) (Supplementary Figure S5). A score of 0 points was associated with 9% mortality, patients with 1–4 points had 9%–32% mortality, and it was 32% for scores $\geq$4. The median value for the Pitt score was 1 (IQR, 0–2; range, 0–10). The AUROC for observed mortality was 0.71 (95% CI: 0.69–0.82) (Supplementary Figure S6). We observed 7% mortality for a score of 0 points, 21.1% for 1–2 and 35.3% for $\geq$3.

As a reference, data for the PROBAC score are provided; here, this score was not applied to exactly the same population was it was derived, as in the derivation cohort we excluded patients who died in the first 48 h, who are included here to provide a comparative estimation to the previous scores. The median value of the score was 4 points (IQR, 3–7; range 0–18). The AUROC for observed mortality was 0.80 (95% CI: 0.79–0.81) (Supplementary Figure S1). Patients with 0 points had a 2% mortality, those with 1 point had 2-20% mortality and those with $\geq$2 had 20% mortality.

The following scores were applied only to specific subsets of patients, more similary to the population in which they were derived. Despite the INCREMENT-ESBL scale was derived from a cohort of patients with ESBL-producing Enterobacteriaceae, we applied it to 4698 patients with bacteraemia due to gram-negative bacteria; their features are shown in Table 3. Mortality at day 30 in this group was 13.4%. The median score was 7 points (IQR, 6–10; range, 0–19). The AUROC for 30-day mortality was 0.81 (95% CI: 0.79–0.82) (supplementary Figure S7). We observed no mortality in patients with 0 points, 0%–18% mortality for 1-4 points and 18% mortality for $\geq$5. The BSIMRS score was applied to 3291 patients with gram negative bacteraemia who had received adequate empirical antibiotic treatment (the same type of patients as it was derived from); their features are shown in Table 3. 30-day mortality was 11.1%. The median score obtained was 4 points (IQR, 2–7; range 0-16). The AUROC for 30-day mortality was 0.72 (95% CI: 0.70–0.75) (Supplementary Figure S8). We observed that a score of less than 3 points predicts a mortality of less than 16%; between 3 and 4 points, between 16% and 22% and a score of 5 or above predicts more than 22%.

Figure 1 shows the calibration plots for all the scores studies, and Table 2 summarises the scores obtained and AUROC.

Discussion

In this study, we evaluated the prediction ability for 30-day mortality of different prognostic scores in a large cohort of patients with bacteraemia; their predictive value for all-cause 30-day mortality was

Table 3. Patients' characteristics in the different subpopulations in which the scores were applied.

Variable	All patients $N = 6313$	Gram negatives $N = 4698$	Gram negatives and active empirical therapy $N = 3291$
Median age in years (IQR)	71 (60–81)	72 (61–81)	72 (61–81)
Male sex	3623 (58.5)	2616 (55.7)	1790 (54.4)
Charlson index median (IQR)	2 (0–3)	2 (0–3)	2 (0–3)
Charlson index age adjusted ≥ 3	3946 (62.5)	2951 (62.8)	2100 (63.8)
Ultimately or rapidly fatal underlying disease	1901 (30.1)	1425 (30.3)	997 (30.3)
Chronic underlying conditions			
Diabetes mellitus	1518 (24)	1130 (24.1)	843 (25.6)
Cancer	1648 (26.1)	1251 (26.6)	92 (28.1)
Hematology neoplasia	432 (6.8)	303 (6.4)	219(6.7)
Liver cirrhosis	548 (8.7)	387 (8.2)	364 (8)
Myocardial infarction	494 (7.8)	348 (7.4)	246 (7.5)
Heart failure	755 (12)	535 (11.4)	374 (1.4)
Chronic pulmonary disease	785 (12.4)	553 (11.8)	398 (12.1)
Dementia	558 (8.8)	439 (9.3)	310 (9.4)
Cerebrovascular disease	666 (10.5)	493 (10.5)	346 (10.5)
Hemiplegia/paraplegia	226 (3.6)	154 (3.3)	104 (3.2)
Chronic kidney disease	855 (13.5)	602 (12.8)	431 (13.1)
Connective tissue disease	192 (3)	135 (2.9)	103 (3.1)
Peptic ulcer	167 (2.6)	118 (2.5)	87 (2.6)
AIDS	49 (0.8)	32 (0.7)	23 (0.7)
Vascular disease	563 (8.9)	384 (8.2)	273 (8.3)
Immunosuppressive treatment	663 (10.5)	491 (10.5)	360 (10.9)
Neutropenia ($\leq$500 cells/μL)	222 (3.5)	169 (3.6)	133 (4)
Source of infection			
Intra-abdominal, non-biliary	539 (8.5)	1937 (41.2)	322 (9.8)
Biliary tract	850 (13.5)	467 (9.9)	615 (18.7)
Catheter-related	769 (12.2)	322 (6.9)	176 (5.3)
Skin and soft tissue	258 (4.1)	112 (2.4)	72 (2.2)
Osteoarticular	73 (1.2)	60 (1.3)	8 (0.2)
Endocarditis	113 (1.8)	21 (0.4)	21 (0.6)
Unknown	810 (12.8)	44 (0.9)	343 (10.4)
Respiratory tract	548 (8.7)	798 (17)	165 (5)
Central nervous system	44 (0.7)	556 (11.8)	8 (0.2)
Urinary tract	2039 (32.3)	252 (5.3)	1511 (45.9)
Other	87 (1.4)	11 (0.2)	45 (1.4)
Aetiology polymicrobial	477 (7.6)	399 (8.5)	284 (8.6)
Aetiology			
S. aureus	557 (8.8)	–	–
Staphylococcus coagulase negative	352 (5.6)	–	–
S. pneumoniae	277 (4.4)	–	–
Enteroccocus spp	345 (5.5)		
Other gram positives	39(0.6)		
E.coli	2702 (42.8)	2701 (57.5)	2092 (63.6)
Klebsiella spp	554 (8.8)	554 (11.8)	409 (12.4)
Other Enterobacteria	362 (5.7)	362 (7.7)	223 (6.8)
P. aeruginosa	195 (3.1)	195 (4.1)	102 (3)
Other gram negatives	556 (8.8)	556(11.8)	259 (7.9)
Anaerobes	330(5.2)	330(7)	206 (6.3)
Fungi	44 (0.7)	–	–
Acquisition site			
Community	2525 (40)	2021 (43)	1580 (48)
Healthcare-associated infection	1653 (26.2)	1247 (26.5)	905 (27.5)
Nosocomial	2049 (32.5)	1372 (29.2)	803 (24.4)
Sepsis severe /septic shock	1708 (27.1)	1267 (27)	965 (29.3)
Pitt index median (IQR)	1 (0–2)	2 (1–3)	1 (0–2)
SOFA index median (IQR)	2 (0–4)	3 (0–6)	2 (0–4)
Appropriate empirical therapy	4220 (66.8)	3656 (77.8)	–
30-day mortality	933 (14.8)	632 (13.45)	406 (12.3)

significant in all cases, but heterogeneous. Overall, predictive scores specifically developed for early mortality in patients with bacteraemia showed higher predictive ability, as expected.

In patients with bacteraemia, Charlson index and its variants are frequently used. Ternavasio-de la Vega et al. found that the updated Charlson score had a better predictive power for mortality than the classical Charlson in patients with *S. aureus* bacteraemia [12]. Schuttevaer et al. found an AUROC of the Charlson score of 0.56 (95% CI: 0.50–0.62) for 30-day mortality and 0.69 (95% CI: 0.66–0.73) for 1-year mortality in patients with bacteraemia attended at the emergency department [13]. These scores only consider chronic conditions, were not derived specifically for patients with bacteraemia but for all

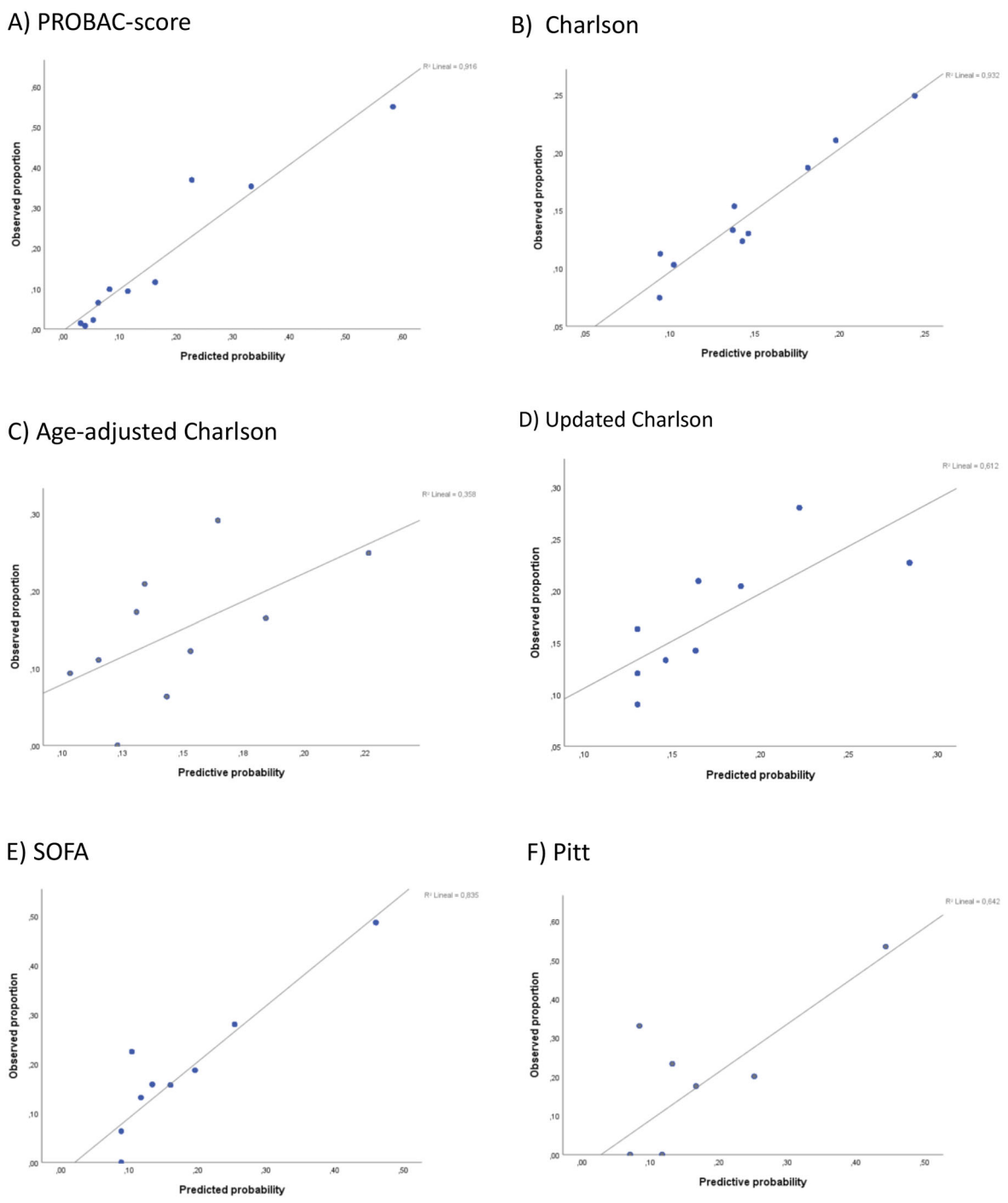

Figure 1. Calibration plots of the different scores for 30-day mortality applied to all patients from the PROBAC cohort (a–f), or to specific subsets of patients: applied to patients with gram negatives bacteraemia (G) and applied to patients with gram negatives bacteraemia and who received active empirical therapy (H).

admitted patients and were studied for 1-year mortality [5–7]. Therefore, we did not expect them to be highly predictive for early mortality in patients with bacteraemia. In this study, Charlson index showed a significant, albeit low predictive ability, confirming the relevance of chronic conditions and age as relevant baseline variables to consider in this patient population. In fact, these variables are frequently included in multivariable models predicting mortality in patients with bacteraemia [14–16].

The SOFA score was developed to assess the severity of organ dysfunction in critically ill patients, and is predictive for mortality in these patients [9]. A SOFA score $\geq$2 is indicative of sepsis, defined as a dysregulated response to infection [17]. The SOFA scale has been externally validated on numerous

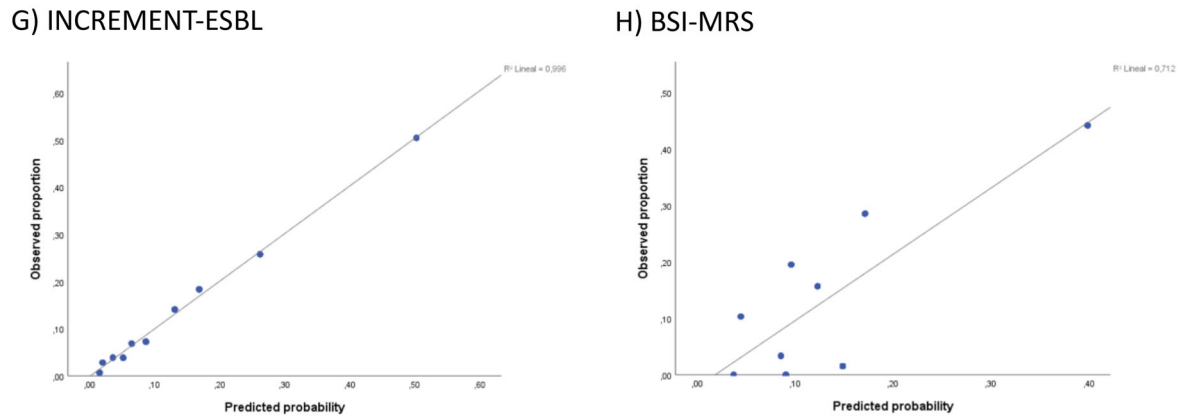

Figure 1. Continued.

occasions to predict the risk of mortality in patients with sepsis and in most recent years, its ability to predict mortality in these patients was compared with that of machine learning-based algorithms [18,19]. Early positive change in SOFA score was associated with 52-week survival in a pilot study including 100 patients with bacteraemia [20]; however, to the best of knowledge, the predictive ability of a baseline SOFA measurement for mortality has not been systematically evaluated in cohorts of patients with bacteraemia.

The Pitt bacteraemia score was developed empirically and applied initially to patients with *Pseudomonas aeruginosa* and *Enterobacter* bacteraemia [8,21], and was later validated for different organisms causing bacteraemia [22]. In the PROBAC cohort, it showed a similar predictive ability to SOFA. Henderson et al. evaluated the predictive ability for 14-day mortality of the Pitt score in the CRACKLE cohort, which included 475 patients with carbapenem-resistant Enterobacteriaceae infections including bacteremic and non bacteremic patients [23]. A Pitt score value $\geq$4 was associated with a mortality RR of 21.9 (95% CI 7.0–68.8) in non-bacteremic patients and of 6.0 (95% CI 2.5–14.4) in bacteremic patients. The Pitt scale was also validated in patients with candidemia, showing an AUROC of 0.74 (95% CI 0.68–0.80) [24]. Finally, Jorgensen et al. found an AUROC of 0.68 (95% CI 0.57–0.80) for mortality in patients with infections caused by carbapenemase-producing Enterobacteriaceae infections treated with ceftazidime-avibactam (only 8.3% were bacteraemic) [25]. Of note, the Pitt score is included as a variable in the INCREMENT-ESBL and BSIMRS scores; however, the PROBAC score did not include it although included 3 parameters which are considered both in SOFA and Pitt scales (respiratory function, hypotension and mental state). Overall, Charlson, SOFA and Pitt scores were less predictive for 30-day mortality than a score developed and internally validated in this cohort (although derived excluding patients who died in the first 48 h); however, the PROBAC score would need to be validated in external cohorts.

Regarding specific populations of patients with gram negative bacteraemia, the INCREMENT-ESBL score showed a high predictive ability despite having been developed specifically for ESBL-producing Enterobacterales. The BSIMRS score, which was previously externally validated in patients with gram negative bacteria receiving active empirical treatment, was also validated in our cohort [26]. However, it was somehow less predictive than the INCREMENT-ESBL score.

It is interesting to note that, in general, the more recently developed scores are more predictive. This is consistent with the fact that, they have been developed in more recent cohorts and with more similar medical conditions to those with we are dealing today.

In general, the utility of the different scores is mostly determined by the complexity of each one of them: it is a fact that scores that include so many variables are not so easily applied at the bedside. This type of scores have value in research to recognise patients with similar characteristics included in different studies. On the other hand, the value of the score at the bedside, lies in the physician's recognition of the variables that are part of the score, which are in his head and help him to recognise high-risk patients.

Some limitations of our study that should be considered, include the fact that our cohort was developed in Spain and the results might not be applicable to other areas with different epidemiology or

management of bacteraemia. The PROBAC score was developed in this cohort and therefore its comparison with other scores has to be taken with caution.We do not consider this to be an external validation of PROBAC score at all. We decided to include it in order to make a comparison with the others scores. Finally, we did not study late mortality. Some strengths include the use of a multicentre, prospectively collected cohort with a high sample size.

In conclusion, all scores evaluated showed some prediction ability for 30-day mortality. However, scores specifically developed for patients with bacteraemia outperformed those which were derived from non bacteremic patients.

Acknowledgements

Members of the PROBAC/GEIRAS-SEIMC/SAMICEI Group: Pilar Retamar-Gentil and José Bravo Ferrer (Unidad Clínica de Enfermedades Infecciosas y Microbiología, Hospital Universitario Virgen Macarena; Departamento de Medicina, Universidad de Sevilla; Instituto de Biomedicina de Sevilla (IBiS)/CSIC, Seville, Spain.; CIBERINFEC, Instituto de Salud Carlos III, Madrid, Spain); Isabel Reche (Servicio de Enfermedades Infecciosas, Hospital Universitario Torrecárdenas, Almería, Spain); Isabel Gea-Lázaro (Unidad de Medicina Tropical, Hospital General de Poniente, Almería, Spain.); Antonio Sánchez Porto (Servicio de Medicina Interna; Hospital Universitario de Puerto Real, Cádiz, Spain); Berta Becerril Carral (Unidad Clínica de Gestión de Enfermedades Infecciosas y Microbiología, Área Sanitaria del Campo de Gibraltar); Esperanza Merino de Lucas (Servicio de Enfermedades Infecciosas, Hospital General Universitario de Alicante, Alicante, Spain; CIBERINFEC, Instituto de Salud Carlos III, Madrid, Spain). Marta Arias-Temprano (Hospital Universitario de León, León), Marcos Guzmán García (Hospital San Juan de la Cruz, Úbeda), Isabel Gea-Lázaro (Hospitalario Ciudad de Jaén, Jaén), Alejandro Smithson-Amat (Hospital de l'Esperit Sant, Santa Coloma de Gramenet, Barcelona, Spain), Antonio Sánchez-Porto, (Hospital del SAS de La Línea de la Concepción, Cádiz, Spain), Alberto Bahamonde-Carrasco (Hospital de El Bierzo, Ponferrada, Spain).

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This work was financed by grants from Plan Nacional de I+D+i 2013– 2016, Instituto de Salud Carlos III, Subdirección General de Redes y Centros de Investigación Cooperativa, Ministerio de Ciencia, Innovación y Universidades (PI16/01432); Spanish Network for Research in Infectious Diseases (REIPI) (RD16/0016/0001; RD16/0016/0008) and cofinanced by European Development Regional Fund 'A way to achieve Europe', Operative Program Intelligent Growth 2014e2020.

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