Usefulness of the NULL-PLEASE Score to predict survival in out-of-hospital cardiac arrest

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Abstract

Purpose: Out-of-hospital cardiac arrest (OHCA) carries a very high mortality even after successful cardiopulmonary resuscitation. Currently, information given to relatives regarding prognosis following resuscitation is often emotive and subjective, and varies with clinician experience. We aimed to validate the NULL-PLEASE score to predict survival following OHCA.

Methods: A multicentre cohort study was conducted, with retrospective and prospective validation in consecutive unselected patients presenting with OHCA. The NULL-PLEASE score was calculated by attributing points to the following variables: **N**on-shockable initial rhythm, **U**nwitnessed arrest, **L**ong low-flow period, **L**ong no-flow period, **p**H<7.2, **L**actate>7.0 mmol/l, **E**nd-stage renal failure, **A**ge ≥85 years, **S**till resuscitation and **E**xtra-cardiac cause. The primary outcome was in-hospital death.

Results: We assessed 700 patients admitted with OHCA, of whom 47% survived to discharge. In 300 patients we performed a retrospective validation, followed by prospective validation in 400 patients. The NULL-PLEASE score was lower in patients who survived compared to those who died (0 [IQR 0-1] vs. 4 [IQR 2-4], p<0.0005) and strongly predictive of in-hospital death (c-statistic 0.874, 95% confidence interval [CI] 0.848-0.899). Patients with a score ≥3 had a 24-fold increased risk of death (OR 23.6; 95%CI 14.840-37.5, p<0.0005) compared to those with lower scores. A score ≥3 has a 91% positive predictive value for in-hospital death, whilst a score <3 predicts a 71% chance of survival.

Conclusion: The easy-to-use NULL-PLEASE score predicts in-hospital mortality with high specificity and can help clinicians explain the prognosis to relatives in an easy-to-understand, objective fashion, to realistically prepare them for the future.

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Abbreviations

CI	Confidence interval
IQR	Interquartile range
NPV	Negative predictive value
OHCA	Out-of-hospital cardiac arrest
OR	Odds ratio
PPV	Positive predictive value
ROC	Receiver operator characteristic curve

Introduction

Out-of-hospital cardiac arrest (OHCA) affects 84 per 100,000 population.[1] In ~28% of individuals, there is return of spontaneous circulation and of these, only 10% survive to 30 days or hospital discharge.[1]

The post-cardiac arrest syndrome, comprising of possible brain injury, myocardial dysfunction, systemic ischaemia/reperfusion response, and the persistent precipitating pathology, often requires resource-intensive monitoring and lengthy treatment in the intensive care unit.[2] Despite the numerous ethical issues which may be involved,[3] an accurate prognostic assessment early in the pathway may be helpful for medical teams to help decision making, to guide families, and to allow allocation of resources to those that are likely to benefit most, in an objective fashion.

Such a scoring system should have high sensitivity (to predict patients with poor prognosis) and high specificity (to ensure all patients with potentially good outcomes are treated).[4,5] Several scores of varying complexity and limited practical application have been developed, and there is currently no recommended simple scoring system for routine clinical use. Yet, we believe that both healthcare professionals and families of patients would wish to know, following OHCA, the likelihood of an individual surviving to hospital discharge. Such a scoring system may be helpful to healthcare professionals and relatives/friends to provide objective, realistic and non-emotive prognostification at such a crucial time.

Currently available risk scores to predict mortality have important limitations. The OHCA Score integrates arrest-related and biochemical variables without patient-specific characteristics,[6] with a c-statistic of 0.88. However, its main limitations is that it is very difficult to calculate, including complex weighting of characteristics and calculation of the natural logarithm of 3 characteristics, making it unpracticable, and it has only been assessed in small cohorts.[6] The ACLS score, developed >30y ago, is difficult to calculate and has relatively poor performance (area-under-the-ROC-curve, AUC 0.786).[7] Similarly, the Graphic Model is very difficult to compute, requires data that are frequently not available (such as minutes to start of CPR or defibrillation) and has not been externally validated.[8] The Prediction Tool is also complex and cumbersome to calculate, and not externally validated.[9] Some scores have only been evaluated in small cohorts,[6,10] some not prospectively assessed,[7,8,10] some not externally or prospectively validated,[8–12] and some only predict survival to 1 month, but not in the hospital setting.[6,9–11] There is therefore an urgent, unmet need for a simple, easy-to-use clinical scoring system to predict survival to hospital discharge, with high sensitivity and specificity.

The NULL-PLEASE score is a relatively new "futility" score to help identify patients who are unlikely to survive following OHCA.[13] The score has only been validated to predict death in the emergency room, with a c-statistic of 0.658.[14] Its usefulness for predicting survival in hospital has not been assessed.

It was our aim to provide independent external validation of the NULL-PLEASE score for prediction of in-hospital survival, in a large cohort of patients with OHCA.

Methods

We performed an external validation of the NULL-PLEASE score in an all-comers population of consecutive patients presenting with OHCA to three large NHS Trusts in England (East and North Hertfordshire NHS Trust, Royal Brompton and Harefield Hospitals NHS Trust and Royal Papworth Hospital, Cambridge) from September 2015 to December 2018, as part of an approved service evaluation with permission from local R&D boards.

NULL-PLEASE Score

The NULL-PLEASE score assigns 2 points to each of the initial arrest characteristics (**N**onshockable rhythm, **U**nwitnessed arrest, **L**ong no-flow or **L**ong low-flow period) and 1 point to each patient characteristic (blood **P**H <7.2, **L**actate >7.0 mmol/L, **E**nd-stage kidney disease on dialysis, **A**ge ≥85 years, **S**till resuscitation, and **E**xtra-cardiac cause). Definitions of individual components of the score are shown in Table 1. As a number of patients did not have lactate or pH measured on arrival, the performance of a modified version of the scoring system excluding these variables, namely the NULL-EASE score, was also assessed.

Data collection

Demographics, descriptive data pertaining to the arrest, initial blood results including pH and lactate, cause of arrest (or presumed cause) and length of hospital stay were documented by clinicians independent of the research team.

Outcome

The primary outcome was in-hospital death or survival to discharge from hospital. The secondary outcome was length of stay.

Statistical analysis

Categorical variables were summarised as proportion (number and percentage) and continuous variables as median with interquartile range (IQR). The association of the NULL-PLEASE score components with the primary outcome was examined using univariate logistic regression analysis. Odds ratios (ORs) with 95% confidence interval (CI) and p-values were obtained for each component and the score as a whole. The predictive ability of the NULL-PLEASE score for the primary outcome was tested using AUC analysis and the c-statistic reported. The same analysis was performed for patients in whom only the NULL-EASE score was available.

Bootstrap re-sampling[15] was used to assess the predictive ability of the score for new data. This has two steps: at the training step, a part of the data is used to fit a logistic regression model, and at the testing step, the estimates of the logistic regression model are used to predict how patients not included in the training set would be classified. The process repeats a thousand times.

A subgroup analysis was performed in patients who had return of spontaneous circulation following the initial arrest and in patients with myocardial infarction as the presumed cause of arrest. Significance was taken as <0.05. Statistical analyses were performed using Stata 15 software (StataCorp, College Station, Texas, USA).

Results

A total of 700 patients were included, 300 in the retrospective and 400 in the prospective validation cohorts. Of the 700 patients, 332 (47%) survived to hospital discharge. Blood pH results were unavailable in 196 patients and lactate was unavailable in 232 patients. The causes of OHCA were myocardial infarction (n=454), pulmonary embolism (n=20), cerebrovascular accident (n=3), bleeding (n=6), trauma (n=9), other causes (n=117) including sepsis, electrolyte disturbances, and 91 unknown. The median length of stay was 5 days [IQR 2-10].

Baseline characteristics of the 300 patients in the retrospective cohort are shown in Table 2. The NULL-PLEASE score was significantly lower in survivors compared to those who died (0[IQR 0-0] vs. 3[IQR 2-5], $p<0.0005$). On univariate logistic regression analysis (Table 2), most components of the score were individually significantly associated with in-hospital mortality, except for gender, end-stage renal failure, extra-cardiac cause and age >85 years, which were under-represented in this cohort. The NULL-PLEASE score was a strong predictor of in-hospital death (c-statistic 0.851, 95%CI 0.808-0.895). We chose a NULL-PLEASE score ≥3 as the optimal cut-point to predict mortality, with sensitivity 50.4% and specificity 94.4% (Figure 1A), with a positive predictive value (PPV) of 86.1% for in-hospital death and negative predictive value (NPV) of 73.6% for survival. Although a score ≥2 had the best combined sensitivity (78.9%) and specificity (84.2%), the cut-point of 3 was chosen to improve specificity, to ensure almost all patients with potentially good outcomes are treated, whilst preserving reasonable sensitivity.

Baseline characteristics of the 400 patients included in the prospective validation cohort are shown in Table 3. The NULL-PLEASE score was significantly lower in those surviving to discharge compared to those who died (0[IQR 0-1] vs. 4[IQR 2-6], p<0.0005). On univariate logistic regression analysis (Table 3), all components of the score were significantly associated with mortality, except for gender and end-stage renal failure, which were under-represented. The score was confirmed to be a strong predictor of in-hospital death (c-statistic 0.8797, 95%CI 0.8471-0.912) in this prospective validation cohort. A NULL-PLEASE score ≥3 had sensitivity 73.5% and specificity 90.3%, with a PPV of 92.3% for in-hospital mortality and NPV of 68.3% (Table 4).

Combining the retrospective and the prospective cohorts, the odds of in-hospital death increased with increasing NULL-PLEASE score (Table 4). Patients with a score ≥3 had a 24-fold increased risk of in-hospital death (OR 23.6; 95%CI 14.87-37.40, p<0.0005) compared to patients with lower scores, with PPV 90.6% and NPV 70.9%. Using logistic regression, a NULL-PLEASE score of 3 was associated with 75% likelihood of death (Figure 1B). Results of bootstrap resampling indicated that the average specificity and sensitivity of a model with NULL-PLEASE score ≥3 when predicting out-of-sample observations was 90.8% and 70.7%, respectively (Table 5).

Subgroup of patients with OHCA secondary to myocardial infarction

Myocardial infarction was the cause of death in 454 patients and 249 (55%) survived to discharge. The score performed well in this group (AUC 0.836, 95%CI 0.80-0.87). Amongst these patients, those with a NULL-PLEASE score ≥3 had a 19-times higher risk of death (OR 19.6; 95%CI 10.3-37.1, p<0.0005) compared to those with lower scores.

The modified NULL-EASE score

Since a number of patients did not have lactate or pH measured on arrival, the usefulness of the modified NULL-EASE score, was also assessed.

In the retrospective cohort, the NULL-EASE score was a strong predictor of death, with AUC 0.819 (95%CI 0.773-0.866). A score ≥3 had a sensitivity of 39.84% and specificity of 96.05%. Similarly, in the prospective cohort, the NULL-EASE score showed an AUC 0.860 (95%CI 0.826-0.894). A score ≥3 had sensitivity of 66.12% and specificity of 90.32%.

Combining the retrospective and prospective cohorts, the NULL-EASE score remained a strong predictor of death (AUC 0.849; 95%CI 0.822-0.876), with a score ≥3 having sensitivity of 57.34% and specificity of 93.37%, PPV 90.6% and NPV 66.4%

NULL-PLEASE score and length of stay

In patients who achieved return of spontaneous circulation following the initial arrest, the median length of stay was 6 days (IQR 3-12). Among these, length of stay was significantly longer in patients who survived compared to those who died in hospital (9[IQR 4-16] vs. 4[IQR 2-7] days, p<0.00005). Using Spearman rank correlation, the NULL-PLEASE score showed weak positive correlation with length of stay in survivors (r=0.248, p<0.0005) and moderate negative correlation in patients who died (r=–0.472, p<0.0005).

Discussion

In this independent external validation in a contemporary cohort of OHCA patients, we show that the NULL-PLEASE score is a strong predictor of in-hospital death, with high sensitivity and specificity. Individuals with a score ≥3 had a 24-fold increased risk of death compared to those with a score of 0-2. A score ≥3 had a 90.6% PPV for in-hospital death, whilst the NPV indicates that a patient with a score <3 has 70.9% chance of survival. Such prognostic information can be very useful for both healthcare professionals and relatives, can be easily and quickly calculated, and easily understood by lay individuals.

Our study provides the most compulsive data yet in support of a risk score to predict survival in OHCA, which is extremely easy-to-use, yet has high sensitivity and specificity, high NPV and PPV, and which has been externally validated, both retrospectively and prospectively, in a very large cohort. With the utilisation of both arrest- and patient-specific characteristics, the NULL-PLEASE score includes vital features associated with adverse outcome.[16]

Importantly, no risk score calculator will be 100% accurate. Experienced clinicians will recognise that not infrequently, patients defy expectations and those thought to have no chance have recovered, whilst some of those predicted to do well, have succumbed. Therefore, such a scoring system can at best serve as an adjunct to decision-making and cannot be used to make decisions on withdrawal of life-supporting treatment in individual patients. It can, however, be used to guide and explain prognosis to relatives who may find that being quoted an objective survival rate based on the score may help better prepare them for the future. Currently, in our experience, information given to relatives is often varied, being frequently both emotive and subjective (for example, wishing to convey hope even in perhaps hopeless scenarios, or predicting gloom to avoid unrealistic expectations by relatives and to prepare them for the worst), and varying with the seniority and experience of the clinician.

The great strength of the NULL-PLEASE score is not only its strong prognostic value, but its simplicity and ease-of-use. It can be calculated on the spot and is easy to interpret. In comparison, both the OHCA and CAHP scores are difficult to calculate, needing advanced calculator functions, or nomograms, and are neither easy to calculate, nor clinically-friendly. Our results support and extend the findings of the initial validation of the NULL-PLEASE score for death in the emergency room in a small cohort,[14] to now predict survival to hospital discharge, in a large independent cohort, with subsequent validation. Since some 55% of OHCAs are attributable to a cardiac cause,[17] the strong performance of the score in this subgroup is highly pertinent. The individual variables in the univariate analysis were highly predictive of outcome, with the exception of variables that were under-represented and thus could not be assessed.

A NULL-PLEASE score ≥3 had a specificity of 92.5%, ensuring most patients with potentially good outcomes are not disadvantaged, with a PPV for in-hospital death of 90.6% with sensitivity 65.8%. In comparison to other scoring systems, an OHCA score[6] ≥32.5 has specificity of only 85% and PPV 96%, sensitivity 46% and specificity 96%. However, the NULL-PLEASE score achieves superior predictive value, and is much easier-to-use.

Although routine blood gas analysis is recommended in patients with OHCA, it is frequently not performed upon arrival, due to the pressures of manpower or time and competing priorities in an emergency situation. Our sensitivity analysis using the modified NULL-EASE score showed a PPV of 90.6% for a score ≥3, similar to that of the NULL-PLEASE score, although sensitivity was lower at 57.3% and NPV only 66.4%. This highlights the importance of measuring pH and lactate upon arrival to optimise the performance of the score.

Although both populations consisted of consecutive all-comers, the retrospective and prospective cohorts differ in some demographic aspects, for example extracardiac cause of arrest 1% vs. 30%, and non-shockable rhythm 11% vs. 36%, respectively, with associated. difference in mortality (41% and 61%, respectively). These differences, are almost certainly due to selection bias in the retrospective cohort, which likely unintentionally excluded patients who may have died very shortly after admission as these cases may not be logged on databases, as we observed when collecting prospective data. However, this underscores the importance of prospective validation of any risk scoring system and specifically the strength of the prospective validation here, which included more patients with extracardiac arrest and with non-shockable rhythm, showing the score to be applicable to different clinical presentations.

The length of stay in our cohort is short compared to a recent UK cohort managed on the intensive care unit,[19] reporting a median stay of 12 days. This is likely due to the unselected nature of our patients, whereas Petrie *et al.* reviewed only patients admitted to the intensive care unit. Even though our median stay is shorter, it still reflects the very significant health economic burden that patients with OHCA place on healthcare systems. When resources are limited, the appropriate allocation of resources to patients that are most likely to survive is essential. We believe our score may be helpful for identifying likely survivors, when optimizing use of finite healthcare resources, although this can only serve as a rough guide. New costly interventions are increasingly subjected to cost-effectiveness evaluations, which will require quantification of the potential benefit, for example the number of additional lives saved. Our score may also be helpful for this purpose.

Limitations

There is inherent bias in the studied population, since these individuals already survived to reach hospital, and we excluded those who died pre-admission. For the variable 'Still resuscitation', meaning ongoing CPR on arrival to hospital, this is very dependent on the particular healthcare system. We are aware that in some places, CPR is almost always continued to hospital arrival (meaning almost every OHCA case will have ongoing CPR on arrival), whereas other systems have prehospital physicians or paramedics who can terminate resuscitation on scene (meaning that only patients with the highest chance of survival are transported to hospital with ongoing CPR, resulting in selection bias). The score incorporates aetiology, namely "E- extra cardiac cause", which in practical terms is frequently not available. In most patients myocardial infarction was the cause of OHCA, and whether the score is equally applicable to patients with other causes of OHCA is unclear. Furthermore, the cause of death was presumed in many cases, without definitive tests, especially in those who died shortly after admission, since in the UK, post-mortems are not routinely performed, with cause of death determined by clinicians based on likelihood, given presentation and comorbidities. Details pertaining to the circumstances of the OHCA and resuscitation are based on documentation and approximation during or post-event, which may be commonly inaccurate.[20,21] In the score, 'Long no-flow period' is defined as no bystander CPR prior to arrival of emergency medical services. However, there are no defined time periods for the no-flow period, it could therefore range from a few to many minutes. Further, although most components of the NULL-PLEASE score performed well individually, end-stage kidney disease was under-represented in our cohort and so conclusions cannot be drawn about the usefulness of this particular component of the score.

An important limitation is that this risk score does not provide information on neurological status on discharge, although there are several available scoring systems to assess the likelihood of good functional recovery on the intensive care unit.[21,22] Lactate and pH were not always available, and the score appears to perform less well without inclusion of these. On the other hand, this reflects real-life scenarios where these measurements are not always available at the time of decision making, highlighting the relative usefulness of the NULL-EASE score. Finally, the score is predictive of outcome in the average patient, not the individual patient. Furthermore, the organization of emergency medical services varies across countries, and our score may need to be calibrated for each specific system.

Conclusion

The NULL-PLEASE score is an easy-to-use clinical scoring system to predict in-hospital mortality in patients with OHCA, with high specificity and high predictive value for in-hospital death. It could be used to support the prognostication process for physicians, and can help clinicians explain the prognosis to relatives in an easy-to-understand, objective fashion, to realistically prepare them for the future.

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