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## **Abstract**

**Background:** We aimed to examine the predictive capacity of easily obtainable risk factors in combination to derive a practical risk scale for predicting older adults at risk of poor outcomes on admission to the emergency general surgical setting.

**Methods:** This is an international multi-center prospective cohort study conducted as part of the Older Persons Surgical Outcomes Collaboration ([www.OPSOC.eu](http://www.OPSOC.eu)). The effect of having hypoalbuminemia (defined as albumin  $\leq 3.5$ g/dL) on selected outcomes was examined using fully adjusted multivariable models. In a subgroup of patients with hypoalbuminemia, we observed four risk characteristics (Male, Anemia, Low albumin, Eighty-five and over [MALE]). Subsequently, the impact of incremental increase in MALE score (each characteristic scoring 1 point (maximum score 4) on measured outcomes was assessed.

**Results:** The cohort consisted of 1406 older patients with median (IQR) age of 76 (70-83) years. In fully adjusted models, hypoalbuminemia was significantly associated with undergoing emergency surgery (1.32 (95%CI 1.03-1.70);  $p=0.03$ ), 30-day mortality (4.23 (2.22-8.08);  $p<0.001$ ), 90-day mortality (3.36 (2.14-5.28);  $p<0.001$ ) (primary outcome), and increased hospital length of stay, irrespective of whether a patient received emergency surgical intervention. Every point increase in MALE score was associated with higher odds of mortality, with a MALE score of 4 being associated with 30-day mortality (adjusted OR(95% CI)=33.38 (3.86-288.7);  $p=0.001$ ) and 90-day mortality (11.37 (3.85-33.59);  $p<0.001$ ) compared to the reference category of those with MALE score 0.

**Conclusions:** The easy to use and practical MALE risk score calculated at point of care identifies older adults at a greater risk of poor outcomes, thereby allowing clinicians to prioritize patients who may benefit from early comprehensive geriatric assessment in the emergency general surgical setting.

## 1.1 Introduction

As the older adult population continues to expand whilst also requiring the greatest proportion of emergency general surgical interventions [1,2], the development of a practical risk scale based upon easily obtainable risk factors to predict morbidity and mortality on admission to the emergency general surgical setting has never been more pertinent. In an observational study of 362 critically ill patients who had emergency gastro-intestinal surgery, pre-operative anemia and hypoalbuminemia were observed to be associated with in-hospital mortality [3].

Anemia is a common and easily obtainable risk factor associated with poor outcomes amongst older surgical patients, such as mortality, higher post-operative complication rates, increased length of hospital stay and worse functional outcomes [4]. Meanwhile, hypoalbuminemia is defined as serum albumin levels below 3.5g/dL; is a non-specific marker of both acute and chronic pathological states such as malnutrition, inflammation, congestive heart failure and hepatic disease [5–7]. In a meta-analysis of 53 cohort studies including patients with an age ranging from 10-89 years, Vincent *et al.*, reported that for every 1g/dL drop in albumin corresponded with 137% increased odds of mortality [5]. Within the general surgical setting, low preoperative albumin levels have also been reported to be associated with complications such as surgical site infections (SSI) and anastomotic leaks post emergency gastrointestinal resection [7–9]. Earlier studies have reported the association between hypoalbuminemia and poor outcomes of older patients, however, an international multi-center study, in the emergency general surgical setting has yet to be reported [5,10–14].

Within our study we have three key objectives; firstly, we aimed to test the association between hypoalbuminemia and poor outcomes in unselected older patients admitted to the emergency general surgical setting, in an international multi-center cohort. Secondly, using a subgroup of patients with hypoalbuminemia, we aimed to test whether

other routinely available characteristics on admission were associated with poor outcomes by conducting an a-priori stratified analysis based on others and own observations. For our third objective, building upon identified characteristics from our second objective, we aimed to test whether these routinely available characteristics on admission could be combined to form a risk scale that predicts which older adults are at a greater risk of poor outcomes.

## **2.1 Materials and Methods**

### **2.2 Study Design**

As part of the Older Persons Surgical Collaboration (OPSOC) <http://www.opsoc.eu>, this prospective study was conducted across five hospitals in the United Kingdom (UK) and one hospital in Ghent, Belgium, between 2013-2016. In line with OPSOC methodology, data were collected within the acute general surgical admission setting for patients aged  $\geq 60$  years consecutively admitted to the participating units throughout May-June (two months) of all four years. Across the six surgical units included, emergency general surgical admissions related to gastrointestinal disturbances i.e. appendicitis, diverticulitis, bowel obstruction/perforation or pancreato-biliary disease, but may have also included surgical conditions such as abscesses. Patients that presented with conditions not pertaining to the gastrointestinal tract; vascular, urological, cardiothoracic, orthopedic or neurosurgical, were admitted under the appropriate specific surgical specialty and thus these patients were thereby excluded from our study. Since 2015, younger patients (<60 years) were included in data collection in OPSOC, but for this study purpose they were excluded. No other inclusion or exclusion criteria were used. Across the six participating emergency surgical units, patients were admitted and managed under the general surgical team, regardless of whether a surgical procedure was actually performed.

## 2.3 Outcomes

The primary outcome was 90-day mortality, whilst secondary outcomes were; 30-day mortality, receipt of emergency surgical intervention, 30-day readmission and length of hospital stay.

## 2.4 Data Collection

Data were recorded and stored in conjunction with local data management standard operating procedures. Anonymized data were collated centrally at the chief investigator's institution. All patients were service users of the state funded point-of-access care provided by the surgical units included, and only routinely available audited data were collected. As such, the collection of the data used in this study was deemed a service evaluation audit which did not require ethical approval, only approval from individual organizations participating in the service evaluation was required and granted.

To characterize co-morbidity, we recorded baseline characteristics, recorded categorically, for the following; anemia ( $<12.9\text{g/dL}$ ), hypoalbuminemia (albumin  $<3.5\text{g/dL}$ ) and polypharmacy ( $\geq 5$  medications) on admission.

All cases were prospectively identified, and baseline data assessed on admission. Follow-up data were obtained via in-hospital electronic records at a later date. A continuous value was recorded, for length of hospital stay (LoS), with days rounded up to the nearest whole day integer. The LoS was arbitrarily re-categorized for ease of interpretation for clinicians, into three dichotomized variables  $<7$  and  $\geq 7$ -days,  $<10$  days and  $\geq 10$ -days and  $<14$  days and  $\geq 14$ -day, which corresponded with approximately the 60<sup>th</sup>, 75<sup>th</sup> and 85<sup>th</sup> centile values of the continuous values. Readmission within 30-day, mortality at 30- and 90-days were also collected.

## 2.5 Theory/Calculation

All analyses were performed using Statistical Package for Social Science (SPSS), version 24.0. Descriptive statistics were compared between participants with hypoalbuminemia vs. normal albumin levels using ANOVA for continuous and the Chi-squared test for categorical data. Logistic regression models were constructed to examine the association between hypoalbuminemia (albumin levels  $>3.5\text{g/dL}$  as the reference category) and each outcome.

For our first objective, using our full cohort which included a mixture of patients with hypoalbuminemia and normal albumin levels ( $n=1406$ ), analyses were carried out using the crude effect of hypoalbuminemia (model A), and adjusted effects of undergoing emergency surgery (model B), and finally adjusted additionally for patient characteristics; age, sex, low hemoglobin, and polypharmacy (model C) [15]. For our first outcome; receipt of emergency surgical intervention, we ran models A and C, with the exclusion of model B (which adjusted for surgical intervention). For all other outcomes, all three models were executed.

In our subgroup analysis for our second objective, including only patients with hypoalbuminemia ( $n=746$ ), we stratified the analyses by selected characteristics, based on others and own observation, to assess their relationship with our study outcomes in order to identify factors which are additionally associated with poorer patient outcomes. The characteristics assessed as the predictor variable were; sex,  $\geq 85$  years, polypharmacy and anemia. The age cut-off of  $\geq 85$  years was selected because this population represent the “oldest old” and are associated with poorer outcomes after abdominal surgery [16]. We constructed logistic regression models in order to assess the predictive potentials of each of these variables against our dichotomized outcomes using the same statistical models described above.

## 2.6 Risk Score Development

For our third objective, the characteristics we identified in our second objective formed the basis for the derivation of MALE risk score; **M**ale, **A**nemic, **L**ow albumin, **E**ighty-five years or over. We assigned one point each for those who satisfied individual characteristics to make up a 5-point score (minimum 0 to maximum of 4 points), in a similar manner as described earlier [17]. Furthermore, in order to ensure goodness of fit of the proposed scoring system, a Hosmer-Lemeshow test was performed [18].

As the MALE score demonstrated internal consistency when applied to the whole cohort, i.e. the risk score performed as expected, the higher the score, the worse the crude rate of outcomes, logistic regression models were constructed to examine the association between MALE score as the predictor variable (with MALE score of 0 as the reference category) and dichotomized outcomes, using our full cohort (n=1406). The following models were constructed; unadjusted (model A), adjusting for undergoing emergency surgery (model B), and additionally adjusting for polypharmacy (model C).

## 3.1 Results

A total of 1658 older patients (aged  $\geq 60$  years) were enrolled between 2013 and 2016 data collection cycles. Of them, 252 cases were excluded due to incomplete data (see Figure 1 for exclusion). Thus 1406 patients were included in the current study. Comparison of basic characteristics between those included and excluded showed similar results. The median age (IQR) of our cohort was 76 (70-83) years, with 378 (26.9%) patients receiving an emergency operation. There were 755 (53.7%) women. When using the albumin cut off of  $\leq 3.5$ g/dL, 746 (53.1%) patients had hypoalbuminemia. The comparison of sample characteristics by albumin categories ( $\leq 3.5$ g/dL and  $> 3.5$ g/dL) are presented in Table 1. There was a similar

likelihood of having hypoalbuminemia between the two sexes ( $p=0.48$ ). Polypharmacy was common in patients with hypoalbuminemia (70%). Nearly two third of patients with hypoalbuminemia also had anemia (63.8%). Characteristic comparisons between groups showed increasing age, polypharmacy, anemia and undergoing emergency surgery, were all significantly associated with having hypoalbuminemia. Almost a third (29.8%) of patients with hypoalbuminemia received emergency surgical intervention, compared to less than a quarter (23.6%) of patients with normal albumin levels ( $p=0.01$ ).

In crude univariate analyses, presence of hypoalbuminemia was associated with receipt of emergency surgical intervention, 90- and 30-day mortality, increased hospital length of stay at all defined cut off points (Table 2). In fully adjusted logistic regression models, having hypoalbuminemia was associated with 90-day mortality (3.36 (95%CI 2.14-5.28);  $p<0.001$ ), 30-day mortality (4.23 (95%CI 2.22-8.08);  $p<0.001$ ), undergoing emergency surgery (1.32 (95%CI 1.03-1.70);  $p=0.030$ ), increased hospital length of stay;  $\geq 7$ -days (1.54 (95%CI 1.22-1.95);  $p <0.001$ ),  $\geq 10$ -days (1.69 (95%CI 1.30-2.19);  $p<0.001$ ),  $\geq 14$ -days (1.84 (95%CI 1.35-2.52);  $p<0.001$ ). Furthermore, in our fully adjusted model focusing solely on patients undergoing emergency surgery ( $n=378$ ), having hypoalbuminemia was associated with our primary outcome of 90-day mortality (3.60 (95%CI 1.15- 11.31);  $p=0.03$ ) (Table 2).

The results of our subgroup analysis confined to older patients with hypoalbuminemia ( $n=746$ ) (Table 3), showed that there are three additional characteristics which were associated with our primary outcome of 90-day mortality in older patients with hypoalbuminemia; **Male** (1.76 (95%CI 1.14- 2.71);  $p=0.01$ ), presence of **Anemia** (1.94 (95%CI 1.19-3.17);  $p= 0.008$ ), **Eighty-five years of age or older** (1.62 (95%CI 1.01- 2.60);  $p=0.048$ ). Based upon these characteristics the MALE risk score was derived, with each characteristic scoring one point, with a potential maximum score of four points.



Of the 1406 patients, 170 (12.1%) had a MALE score of 0, 427 (30.4%) had a MALE score of 1, 499 (35.5%) had a MALE score of 2, 272 (19.3%) had a MALE score of 3 and 38 (2.7%) had a MALE score of 4. Figure 2a displays the relationship between increasing MALE score and the incidence of poor outcomes occurring. For every point increase in MALE score, there is a corresponding incremental linear increase in the number of patients that died at 90- and 30-days. Figure 2a also shows that after a MALE score of 2, there is a linear increase in 30-day readmission rates. From a MALE score of 0-3, Figure 2a demonstrates a corresponding increase in the number of patients remaining in hospital greater than or equal to the median length of hospital stay.

Similarly, in a sub-group of only patients undergoing emergency surgery (n=378) (Figure 2b), every point increase in MALE score corresponded with an increase in the number of deaths at 90- and 30-days. The application of the MALE risk score against study outcomes is displayed in Table 4.

MALE scores of >1 with every point increase were associated with higher odds of mortality, with a MALE score of 4 being associated with 90-day mortality (fully adjusted OR(95% CI)=11.37(3.85-33.59);  $p<0.001$ ) and 30-day mortality (fully adjusted OR(95% CI)=33.38(3.86-288.68);  $p=0.001$ ). A MALE score >1 was associated with greater than median length of stay (>5days) up to a MALE score of 3 (fully adjusted OR(95% CI)=2.37(1.56-3.60);  $p<0.001$ ), however this association was lost at a MALE score of 4. Only a MALE score of 4 was associated with 30-day readmission (adjusted OR 2.41 (95%CI 1.10-5.25);  $p<0.028$ ).

Figure 3a and b displays the  $\log_2(x)$  of odds ratios with confidence intervals, based on results from Table 4, model A. The results of Figure 3a display each point increase in MALE score coinciding with increased odds of mortality at 30- and 90-days in an incremental linear

fashion. Figure 3b shows that for every point increase in MALE score after a score of 2 there was a corresponding, linear increase in odds of 30-day readmission. The odds of remaining in hospital greater than or equal to the median length of hospital stay also expresses a linear step-wise relationship with increasing MALE score, however a MALE score of 4 had slightly reduced odds when compared to a MALE score of 3.

#### 4.1 Discussion

Hypoalbuminemia is prevalent in older acute surgical patients, with over half of older patients admitted having albumin levels  $\leq 3.5$ g/dL. Even at this conservative cut off, we observed that hypoalbuminemia was associated with excess mortality and increased length of hospital stay, irrespective of whether patients received an emergency operation. Nevertheless, in a sub-group of only patients that received an emergency gastro-intestinal operation, we observed that hypoalbuminemia was only associated with 90-day mortality. Moreover, we aimed to examine the predictive capacity of easily obtainable point-of-care variables in combination to derive a practical risk scale for predicting older adults at risk of poor outcomes on admission to the emergency general surgical setting. We have shown that the MALE risk score; **M**ale, **A**nemic, **L**ow albumin and being **E**ight-five years of age or older, is not only practical and easy to calculate, but it is also an accurate predictor of poor outcomes in older adults on admission to the emergency general surgical setting.

We confirmed earlier reports on the association between hypoalbuminemia as a predictor of poor outcomes on admission to the emergency setting [6,13], but in a multi-center international cohort, irrespective of whether patients received an emergency operation. Additionally, we analyzed a sub-cohort of only patients that received an emergency operation (Table 2). We observed that patients with hypoalbuminemia were at increased odds of

undergoing emergency surgery (Table 2). This is likely due to these patients experiencing protein-losing enteropathy as a consequence of increased mucosal permeability found in pathologies such as inflammatory bowel disease, intestinal infection and bowel malignancy [19]. Earlier studies have reported the association between hypoalbuminemia and post-operative complications such as anastomotic leaks and surgical site infections [7,8]. Whilst we did not record the incidence of these complications, we did record surrogate markers of surgical complications such as increased length of hospital stay and 30-day readmission. However, we did not observe an association between pre-operative hypoalbuminemia and an increased length of hospital stay nor 30-day readmission in the patients that received an emergency operation (Table 2). Furthermore, whilst earlier studies have reported the association between hypoalbuminemia and 30-day mortality in patients that had an emergency operation [3,9], we only observed an association between hypoalbuminemia and 90-day mortality post-emergency operation. This may be due to the range of emergency gastro-intestinal procedures included within our study, which may suggest that certain gastro-intestinal procedures in patients with hypoalbuminemia pose a greater risk of earlier complications. Future research is required to elucidate this point.

Numerous randomized controlled trials have investigated the impact of human albumin transfusions in the treatment of hypoalbuminemia [5,20,21]. However, the benefit of albumin replacement in patients with hypoalbuminemia remains inconclusive [5]. In a systematic review of 17 randomized trials, which investigated the benefit of pre-operative carbohydrate loading on patient outcomes, Bilku et al., reported that it had a positive influence on a wide range of perioperative markers of clinical outcome [22]. In a similar respect, this raises the question as to whether high protein dietary loading in patients with hypoalbuminemia, akin to carbohydrate loading, may have a beneficial effect.

In accordance with our secondary objective, we aimed to identify other easily obtainable point-of-care risk factors which could be combined to form a risk score, for differentiating which older patients are at a greater risk of poor outcomes on admission (Table 3). We showed that the proposed MALE risk score was able to predict the incremental increased risk of 30- and 90-day mortality, 30-day readmission and an increased length of hospital stay, with every point increase (Table 4). The utility of the MALE score for emergency surgeons is accentuated by the fact that older patients have the greatest demand for surgical procedures, with the rate of surgical procedures performed on older patients exceeding the rate of population growth in the UK [23–25]. The MALE score assessed on admission holds the potential of allowing doctors in training and surgeons to more accurately tailor patient centered care post-operatively whilst also giving emergency surgeons the opportunity to make pre-emptive adjustments, including early comprehensive geriatric assessment. Comprehensive geriatric assessment is an established and evidenced based method of evaluating and optimizing physical, psychosocial, functional and social issues in older adults [26]. In a Cochrane systematic review of eight randomized controlled trials, Eamer *et al.*, found that comprehensive geriatric assessment in the surgical setting was associated with reduced mortality, a reduction in the discharge of patients to an increased level of care and a slight reduction in hospital length of stay [27]. Thus, the MALE score would allow clinicians to prioritize older adults in need of early comprehensive geriatric assessment, in the face of increasing numbers of older adults admitted to the emergency general surgical setting, coupled with the reality of limited multi-disciplinary team availability.

The MALE score offers a number of advantages for the clinician over other risk scoring systems. Firstly, unlike the American College of Surgeons, National Surgical Quality Improvement Programme risk calculator, the MALE score is easy and quick to calculate as it relies only on four easily obtainable patient characteristics and is therefore more useful for

the busy doctor in training and surgeon in identifying older adults in need of comprehensive geriatric assessment early. Furthermore, although the P-POSSUM is useful in the adult population, the scoring system is not generalizable to older adults [28]. Thirdly, whilst the APACHE score is accurate and reliable for research purposes, it is nevertheless impractical and is rarely used in the clinical setting.

Our study benefits from a number of strengths. These include; large sample size, consecutive unselected data collection during study periods and an international multicenter study design. We were able to control for important prognostic markers and the association observed were independent of these variables.

We acknowledge the limitations of all non-randomized study designs. Data were not collected on individual co-morbidities and therefore we cannot be certain that the association between having hypoalbuminemia and mortality and increased length of hospital stay are not being driven by other factors such as malignancy. However, we were able to adjust for polypharmacy, low hemoglobin and albumin which are all highly related to co-morbid burden and these serve as surrogate markers of severity of existing chronic and acute co-morbid burden, thus perhaps a better measure of co-morbidities compared from simple yes/no which merely state presence of a diagnosis rather than effect the individual had due to the diagnosis. Our study may suffer from selection bias due to data only being collected between May-June of each year, despite the inclusion of all unselected older adults admitted to the emergency surgical setting. Because only routinely available data were collected for audit purposes, we were limited in the variables we could include in our risk scale. Nevertheless, as these variables are routinely available, this allows for the application of the risk scale without the need for additional tests. Data on the indication for admission or the type of emergency surgical procedure carried out were not collected.

This is the first study to propose a more practical risk scale for older adults admitted to the emergency general surgical setting, using only four easily obtainable patient characteristics at the point-of-care. We demonstrated the linear relationship between the incremental increase in MALE score point and poorer outcomes such as mortality, hospital readmission and increased length of hospital stay. The MALE risk score will allow clinicians to prioritize patients for comprehensive geriatric assessment – which has been shown to improve patient outcomes in the surgical setting.

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