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Systematic Review / Meta-analysis

Hierarchical regression of ASA prediction model in predicting mortality prior to performing emergency laparotomy a systematic review

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ABSTRACT

Background: In light of increasing litigations around performing emergency surgery, various predictive tools are used for prediction of mortality prior to surgery. There are many predictive tools reported in literature, with ASA being one of the most widely accepted tools. Therefore, we attempted to perform a systematic review and meta-analysis to conclude ASA's ability in predicting mortality for emergency surgeries.

Methods: A wide literature search was conducted across MEDLINE and other databases using PubMed and Ovid with the following keywords; "Emergency laparotomy", "Surgical outcomes", "Mortality" and "Morbidity." A total of 3989 articles were retrieved and only 11 articles met the inclusion criteria for this meta-analysis. Data was pooled and then analysed using the STATA 16.1 software. We conducted hierarchal regression between the following variables; mortality, gender, low ASA (ASA 1–2) and high ASA (ASA 3–5).

Results: 1. High ASA was associated with a higher rate of mortality in males with '*p*' value of 0.0001 at alpha value of 0.025. 2. The female gender itself showed a significantly high mortality rate, irrespective of low ASA or high ASA with '*p*' value of 0.04 at alpha value of 0.05. 3. ITU admissions with a high ASA had a greater number of deaths compared to low ASA. '*p*' value of 0.0054 at alpha value of 0.01.

Conclusion: Higher ASA showed a direct association with mortality and the male gender. The female gender was associated with a higher risk of mortality regardless of the ASA grades.

1. Introduction

Various tools such as ASA, P-Possum, Frailty Index and APACHE have been used for predicting morbidity and mortality prior to performing emergency laparotomy.

ASA is a widely used predicting tool which has undergone various reviews since its development in 1941 [1–3]. The intention of this model is to classify patients' physical fitness before surgery. ASA is classified into 6 different subgroups, ASA 1–6, and is defined from a healthy patient (ASA 1) to a patient who is not expected to survive without the operation (ASA 5) and ASA 6 where the patient is declared brain dead as shown in Table 1 [4–6].

POSSUM (Physiologic and Operative Severity Score for the Study of Mortality and Morbidity), was widely recommended for surgical practice [7–9]. It was initially introduced in 1991 [10] and used 62 variables (48 physiological and 14 surgical) [11]. Overtime these variables were reduced to 12 physiological and 6 surgical factors. This scoring system predicts morbidity and mortality in the first 30 post-operative days and allows for a comparison within the institutions as well as with other institutions [10]. This method was used for a large number of patients and the results showed that this scoring system overestimated mortality, especially in the case of low risk patients. Hence the P-POSSUM score (Portsmouth Physiologic and Operative Severity Score for the Study of Mortality and Morbidity) was developed. P-POSSUM uses the same

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Table 1
ASA scoring system classifications.

Class	Definition	Examples
1	Normal health	Healthy, non-smoking, no or minimal alcohol use
2	Mild systemic disease	Mild diseases only without substantive functional limitations. Examples include (but not limited to): current smoker, social alcohol drinker, pregnancy, 30 < BMI < 40, well-controlled DM/HTN, mild lung disease
3	Severe systemic disease	Substantive functional limitations. One or more moderate to severe diseases. Examples include (but not limited to): poorly controlled DM or HTN, COPD, morbid obesity (BMI ≥ 40), active hepatitis, alcohol dependence or abuse, implanted pacemaker, moderate reduction in ejection fraction, ESRD undergoing regularly scheduled dialysis, premature infant PCA < 60 weeks, history (>3 months) of MI, CVA, TIA or CAD/stents
4	Severe systemic disease that is a constant threat to life	Examples include (but not limited to): recent (<3 months) MI, CVA, TIA or CAD/ stents, ongoing cardiac ischaemia or severe valve dysfunction, severe reduction in ejection fraction, sepsis, DIC, ARD or ESRD not undergoing regularly scheduled dialysis
5	Moribund: survival not expected without surgery	Examples include (but not limited to): ruptured abdominal/thoracic aneurysm, massive trauma, intracranial bleed with mass effect, ischaemic bowel in the face of significant cardiac pathology or multiple organ/system dysfunction
6	Brain-dead organ donor	

variables as the POSSUM system but it is able to reduce the over-estimated mortality [11,12]. The P-POSSUM is calculated by adding a regression equation to the POSSUM calculation [13].

Frailty index (also known as Rockwood Scoring System) is another popular scoring system, which measures the health status of older individuals. It determines the trend between ageing and vulnerability in comparison to poor outcomes. This tool was developed by Dr Kenneth Rockwood and Dr Arnold Mitnitski at Dalhousie University in Halifax, Nova Scotia, Canada. It is a proportion of deficits present in patients out of the total number of age-related health variables considered [14], distinguished from the ageing process and comorbidity [15]. This system can help with various outcomes, including postoperative morbidity and mortality, intensive care survival and post-discharge status [16]. Although initially designed for determining the need for social support for medical patients prior to discharge, it is now being adapted by the surgical community to assess pre-operative mortality risk.

The APACHE (Acute Physiology and Chronic Health Evaluation) scoring system uses 34 physiological variables to assess disease severity. The APACHE system was soon replaced by APACHE II, which uses only 12 variables, including both physiological and laboratory measurements, and added variables for age and prior health status [17]. The APACHE II scoring system was designed for intensive care units, as a predictor for perioperative events in patients undergoing various surgeries [18].

The aim of this meta-analysis is to assess the practicality and effectiveness of ASA in predicting mortality prior to performing emergency laparotomy.

2. Methods

2.1. Search strategy

We searched MEDLINE and other databases using PubMed and Ovid with the following key words and search filters for human studies. Key words: "Emergency laparotomy", "Surgical outcomes", "Mortality" and "Morbidity." No language restrictions were applied. We focused mainly on the emergency laparotomy data published in the literature, looking at the mortality and predictive models. The work has been reported in line with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [19] and AMSTAR (Assessing the methodological quality of systematic reviews) Guidelines [20]. This study is registered with the ResearchRegistry and the unique identifying number is: reviewregistry1028 [21]. This was to ensure high methodological rigour. This retrieved 3989 relevant articles. 37 articles were removed as they were duplicates.

A further 3681 articles were removed, as their titles were irrelevant to the study resulting in 271 studies remaining.

2.2. Study selection

2.2.1. Inclusion criteria

The following variables were used for the inclusion criteria: (1) Presence of predictive model; (2) Publication between 2008 and 2019; (3) Presence of laparotomy data; (4) Presence of mortality data; (5) Randomised Clinical Trials (RCT); (6) Prospective studies; (7) Retrospective studies; (8) Cohort studies; (9) Full papers; (10) English papers only.

2.2.2. Exclusion criteria

The following variables were used for the exclusion criteria: (1) Lack of predictive models; (2) Publications prior to 2008; (3) Lack of clear laparotomy data; (4) Lack of mortality data; (5) Emergency and non-emergency comparison (all elective surgery data); (6) Systematic reviews; (7) Descriptive/narrative reviews; (8) Previous meta-analysis; (9) Non-English papers; (10) Abstracts without full paper; (11) Absence of abstract; (12) Subjective model (arbitrary estimation of mortality and morbidity without use of tools); (13) Not relevant.

Out of the remaining 97 articles, another 74 were excluded due to non-replicable predictive models and articles with predictive models other than ASA. This resulted in 23 papers [22–44], which were used for the qualitative synthesis. Lastly, 12 papers were excluded from the statistical analysis because they contained another predictive model with ASA, or the ASA data was unclear or incomplete (to avoid high risk of bias). Finally, 11 papers [22,24,25,28,31–33,36–38,43] were included for the purpose of the statistical analysis.

The process of study selection is outlined in the PRISMA flowchart (Fig. 1).

2.3. Statistical analysis and modelling

We used STATA 16.1 to conduct hierarchal regression of the variables and we summarised our results in three separate sections. We also reported the results as means, medians, standard deviations, and confidence intervals.

2.4. Subgroup analysis

We conducted subgroup analysis based on 4 papers [27,32–34] with the ASA model, and ITU admission as the criteria; whether it affects mortality or not depending on the ASA grades.

3. Data synthesis

3.1. Data pooling

3.1.1. Stratification

Stratification strategy was applied in the study selection process by taking the 97 papers and stratifying them into the following four categories: (1) ASA; (2) P-Possum; (3) Frailty Index; (4) APACHE. This led to the selection of final 11 studies for this meta-analysis (Table 2).

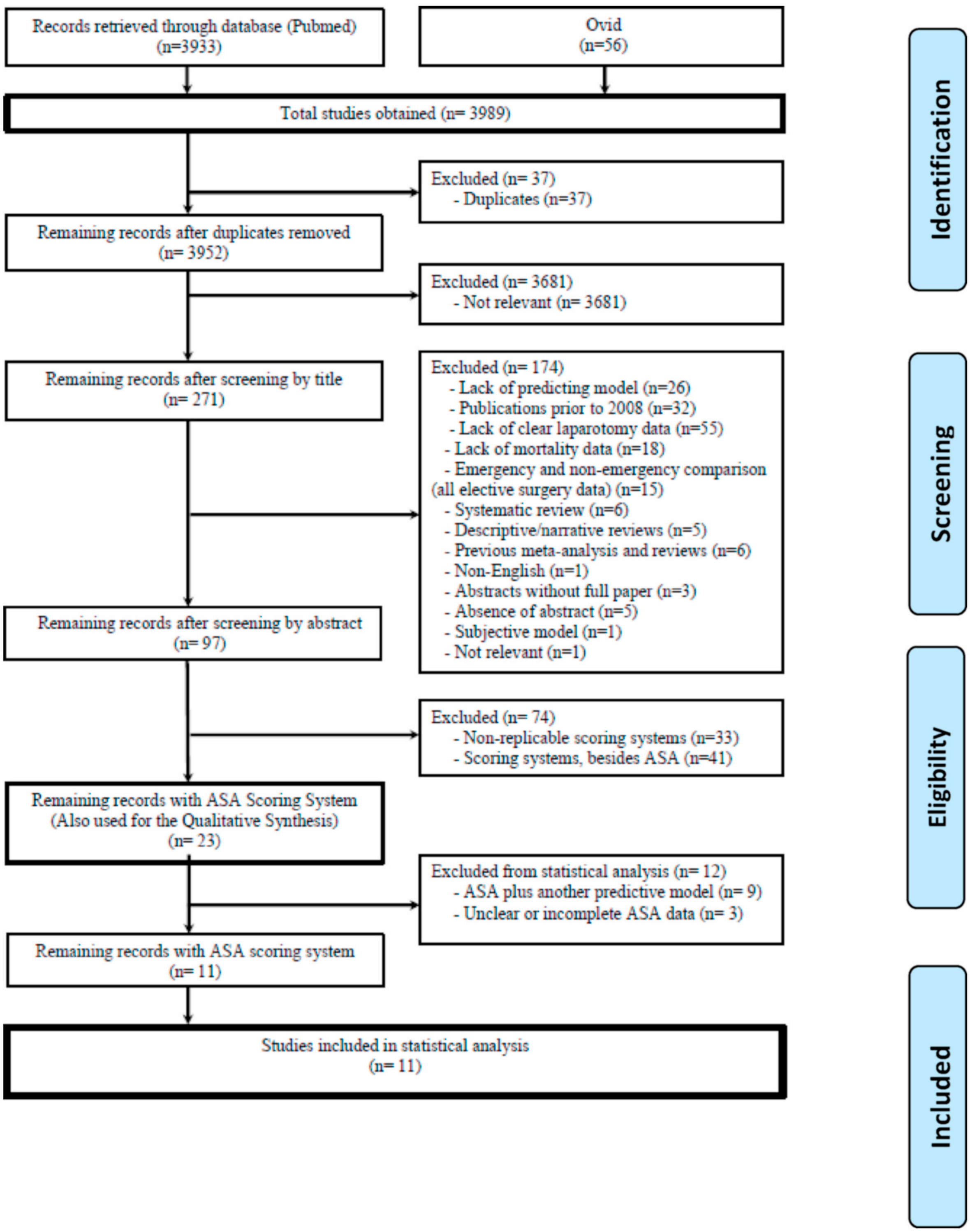

Fig. 1. Prisma flow diagram.

3.1.2. Matching

11 papers with the ASA predictive tool, ranging from ASA 1 to ASA 5, relating to mortality as the outcome were matched together.

The following variables were used to collect the data from the 11 studies: (1) Author; (2) Year of Publication; (3) Total number of patients; (4) Mortality figures reported; (5) Gender; (6) Low ASA (ASA 1–2); (7) High ASA (ASA 3–5).

3.1.3. Combining

Upon a discussion among the authors conducting the meta-analysis, an agreement was achieved to combine the papers as ASA 1–2 being "low ASA" and ASA 3–5 being "high ASA". We agreed to disregard ASA 6 since it is inappropriate for our meta-analysis.

For the subgroup analysis, papers were collated with ASA as the predictive tool for mortality and the papers included data regarding ITU admissions (Table 3).

Table 2
Included studies based on ASA predicting tool.

Author	Year	Patients	Mortality	Male	Female	Low ASA	High ASA
Tengberg et al. [33]	2017	1139	230	534	605	615	524
Becher et al. [22]	2016	215	57	123	92	23	192
Shidara et al. [31]	2016	8414	170	4415	3999	7247	1167
Lees et al. [28]	2015	257	31	134	123	54	203
Masuda et al. [38]	2015	103	15	42	61	48	35
Wilson et al. [43]	2014	73	28	23	50	21	52
Gul et al. [24]	2012	131	3	61	70	76	55
Harries et al. [25]	2012	129	25	63	66	70	59
Ozkan et al. [36]	2012	190	6	123	67	95	95
Tan et al. [37]	2011	104	5	65	39	72	32
Ozkan et al. [32]	2010	92	14	48	44	54	38
Total:		10,861	584	5631	5216	8375	2472

Table 3
Included studies for the subgroup analysis.

Author	Year	Patients	Mortality	Male	Female	Low ASA	High ASA	ITU Admission
Tengberg et al. [33]	2017	1139	230	534	605	615	524	274
Vester-Anderson et al. [34]	2014	2904	678	1411	1493	1587	1299	452
Lal et al. [27]	2012	80	18	28	52	32	35	18
Ozkan et al. [32]	2010	92	14	48	44	54	38	22
Total:		4215	940	2021	2194	2288	1896	766

4. Results

The results are subdivided into 3 sections:

Section 1 - Hierarchical regression between ASA, mortality and the male gender.

Section 2 - Hierarchical regression between ASA, mortality and the female gender.

Section 3 - Subgroup analysis for ASA, mortality and ITU admission.

4.1. Section 1

4.1.1. Model 1

Hierarchal regression was conducted using mortality as the dependent variable vs the male gender as the independent variable, which showed statistically insignificant mortality with a '*p*' value of 0.051.

4.1.2. Model 2

Hierarchal regression was conducted using mortality as the dependent variable vs the male gender and low ASA as the independent variables.

Hierarchical regression (Model 2 – Model 1) showed significant function change with a '*p*' value of 0.005 (R-squared: 0.7645). Although the function change is significant, a 't' value of low ASA is '-3.7'. This shows that low ASA has a negative association with mortality and the male gender. (Stata Output - 1).

4.1.3. Model 3

Hierarchal regression was conducted using mortality as the dependent variable vs the male gender, low ASA and high ASA as the independent variables, which showed significant function change with a '*p*' value of 0.0001 (R-squared: 0.9687). This shows that the male gender and low ASA are not significant, but high ASA showed a significant '*p*' value (0.0001) and a 't' value of '6.76'. This means that high ASA is a contributing factor for mortality in males and therefore has a positive association with their mortality. The male gender shows negative distribution with a 't' value of '-3.47' when high ASA was introduced into the model.

4.2. Section 2

4.2.1. Model 1

Hierarchal regression was conducted using mortality as the dependent variable vs the female gender as the independent variables, which showed statistical significance with a '*p*' value of 0.04.

4.2.2. Model 2

Hierarchal regression was conducted using mortality as the dependent variable vs the female gender and low ASA as the independent variables. Function change was significant between.

Model 2 and Model 1 with a '*p*' value of 0.0001. But the 't' distribution for the low ASA was '-11.41'. This shows that low ASA has a negative distribution with the female gender.

4.2.3. Model 3

Hierarchal regression was conducted using mortality as the dependent variable vs the female gender, low ASA and high ASA as the independent variables. This showed insignificant function change with the '*p*' value of 0.532 (R-squared: 0.9668). It also shows that the addition of high ASA with the female gender does not show any significant effect on mortality.

Although low ASA with the female gender shows significant function change, this is not the case with the addition of high ASA where the function change was insignificant. When it comes to the distribution of the data of ASA with the female gender vs mortality, both low ASA and high ASA have negative distributions. Therefore, ASA itself may not have any association with mortality rate of the female gender. (Stata Output - 1).

4.3. Section 3

Subgroup analysis

We conducted hierarchal regression to see whether any differences between low ASA and high ASA were present in predicting mortality figures when patients were admitted to ITU.

4.3.1. Model 1

Mortality was used as the dependent variable vs low ASA and ITU admission as the independent variables for the baseline model. This showed significant '*p*' value of 0.0185 (R-squared: 0.9997).

4.3.2. Model 2

Hierarchal regression was conducted using mortality as the dependent variable vs low ASA, ITU admission and high ASA as the independent variables. This showed '*p*' value of 0.0054 (R-squared: 1.0000) with a 't' value of '-2.68'. This model shows that the high ASA and ITU admission have negative association with mortality.

Hierarchal regression could not be performed with additional variables (such as gender) due to the small sample size, which resulted in model failure. Therefore, we reassigned our 'α' value for the hierarchal regression analysis as 0.01, which means prediction of 1 death out of a 100 ITU admissions. At this level of 'α' significance, we reinterpreted our results of the subgroup analysis, which now shows that the high ASA has significant mortality with a '*p*' value of 0.0054. After assigning the new 'α' value of '0.01' the low ASA and mortality rate in ITU admission resulted with a '*p*' value of 0.0185, which is not significant anymore because '*p*' value is greater than 'α' value. (Stata Output - 2).

5. Discussion

Since 1941, ASA has been used as a predicting tool for preoperative health of surgical patients. It plays a vital role in distinguishing patients' post-surgical outcomes. ASA is classified into 6 different subgroups, ASA 1–6, and is defined from a healthy patient (ASA 1) to a patient who is not expected to survive without the operation (ASA 5) and ASA 6 where the patient is declared brain dead. The aim of this meta-analysis is to determine the suitability of ASA in predicting mortality for patients undergoing emergency laparotomy, and risk stratification for ITU admission. ASA 6 was disregarded as it is inappropriate for this meta-analysis.

For the meta-analysis, we chose the last 10 years (2008–2019) to search the published literature to keep uniformity across the data due to the technological advancements made in 2008 relating to the laparotomy facilities. Several databases such as MEDLINE were searched using PubMed and Ovid with "Emergency laparotomy", "Surgical outcomes", "Mortality" and "Morbidity", as the keywords with search filters for human studies. No language restrictions were applied. We focused mainly on the emergency laparotomy data published in the literature, looking at the mortality and predictive models such as ASA, P-Possum, Frailty Index and APACHE II. Due to our use of multiple search engines in efforts to be thorough, we encountered duplicate articles which were subsequently removed; this led to reduction of the initial 3989 articles to 3952 articles.

At this point we began a series of rigorous steps to ensure all articles met the precise inclusion and exclusion criteria defined by the team. The process began with an initial review of each article by its title which resulted in a substantial decrease to 271 articles. The 3681 articles were excluded due to their lack of relevance, as we were mainly interested in emergency laparotomy data. The next step included meticulous reading of the abstracts of each article to ensure relevance, and the following inclusion and exclusion criteria were met.

All publications prior to 2008 as well as those not in English were excluded (n = 33). 5 of the articles did not have an abstract for us to read and therefore were omitted. We excluded 26 papers due to lack of a predictive model, 55 papers due to lack of clear laparotomy data and 18 papers due to lack of mortality data. The main intention of this meta-analysis is to research a trend within the emergency setting therefore any papers pertaining to elective procedures were also excluded (n = 15). Systematic reviews, descriptive/narrative reviews, subjective models, previous meta-analysis and reviews were also excluded at this point (n = 17). Another 3 articles were removed due to the absence of full texts. Unfortunately, we did not find any relevant RCTs and case control studies. At the end of the study selection process, we were ultimately left with 97 papers for further review. After removal of non-replicable scoring systems, and other predictive tools beside ASA, we were left with 23 articles. These 23 articles were used for the qualitative synthesis. Of these, another 9 were excluded due to the use of multiple predictive models along with ASA, and 3 were removed due to unclear or incomplete ASA data. This ultimately left us with 11 articles for our systematic analysis.

The majority of studies either had ASA data in separate categories 1, 2, 3, 4, 5 or low ASA as ASA 1, 2 and high ASA as ASA 3, 4, 5. As mentioned previously, we also adopted the method of grouping ASA in two categories of low (ASA 1, 2) and high (ASA 3, 4, 5).

Within our data, we found there was a significant difference between the number of patients found in each paper. For example, Shidara et al. [31] used over 8000 patients in their study, compared to Wilson et al. who had fewer than 100 patients. This resulted in a skewed distribution of data, which also resulted in differences in reporting of mortality figures and subsequent results of this analysis.

We also collected data on procedures, colectomy, adhesiolysis, Hartmann procedure, other procedures, small bowel obstruction, small bowel resection, non-malignant intestinal obstruction, large bowel resection, bowel resection (non-specified), anastomotic leak, abscess, bleeding, contamination, malignancy, ischaemia, overall 30-day survival rate, fistula, gastrointestinal perforation, and other findings.

One of the key limitations in the data analysis phase was the lack of homogenous data found in the original articles. This meant that each author had prioritised their data uniquely, which meant that extracting it for our meta-analysis, to compare homogenous data became a challenge. For example, Sharrock et al. [42] had clear data surrounding patients in which malignancy was found, however the majority of other papers did not include this information. Tengberg et al. [33] mentioned some findings during laparotomy such as gastrointestinal perforation, obstruction, anastomosis and bleeding, however did not mention malignancy. Khan-Keil et al. [26] focused on the types of resections performed during laparotomy such as Hartmann procedure, colectomy or other bowel resections.

While performing hierarchal regression with gender, mortality, and ASA grade we noticed that the degree of freedom was only 11. Papers included in the hierarchal regression did not provide specific mortality figures in relation to each gender, which is a limitation faced by this meta-analysis.

We found that the higher ASA has a direct relationship with mortality and the male gender. However, we also found that there was no association between mortality and independent factors (the female gender, low ASA, high ASA). These findings suggest that the female gender had no correlation with mortality.

In regard to the subgroup analysis, it is also perceived that high ASA had significant mortality as opposed to low ASA regardless of ITU admission for either ASA grades. Therefore, we concluded from the ITU admission that high ASA had a greater number of deaths compared to low ASA. As a result, our study reinforces that higher ASA grades admitted to ITU are associated with increased mortality following emergency laparotomy. Although, the fact that mortality is directly related to ASA score is not surprising [45,46], the gender associations revealed in this meta-analysis are a novel finding. Our study suggests that patients' outcome may be predetermined by their ASA grade, specifically for males, if admitted to ITU. It should be mentioned that ASA, despite being a statistically significant variable, with our relatively small data set, we cannot accurately describe the direct magnitude of its power to predict mortality. However, it does highlight the importance that we should take higher ASA candidates seriously and admit patients to the appropriate level of care after surgery. Higher level monitoring and care within an intensive care unit or extended recovery room should be made available to try and provide the best outcome for the patient. Especially in the case of the aging population, where age provides another dimension for poorer outcomes [47]. The mortality rate of 22.3% from our cohort is relatively high but it may reflect our inclusion of ITU admissions which would naturally attract patients requiring greater post-operative care and higher risk of dying [34].

While performing hierarchal regression in the subgroup (ITU admission), the degree of freedom was either 3 or less than 3. There was a lack of mortality data for the ITU group in relation to ASA grades, so we conducted hierarchal regression by creating statistical models with and without high ASA and low ASA. Through this process we identified that upon addition of the female gender variable; the 'function change' was insufficient and was therefore unable to achieve the significant difference between low ASA and high ASA, which was not the case with the male gender. At this stage, we are unable to conclude why there is a difference between both genders when admitted to the ITU. Further case control trials and/or randomised case control studies are ideal for determining the gender inequality in mortality for ITU patients. As this is a retrospective study, further prospective data collection on emergency laparotomy would be beneficial to confirm the findings. No patient inclusion bias was known.

Patients who underwent emergency laparotomy with lower ASA grade showed significantly lower mortality rate compared to those with higher ASA. The main factor influencing ASA grade is the disease severity therefore, keeping systemic diseases under control can result in a significant improvement in mortality.

6. Limitations

1. Study selection did not include non-English articles.
2. Lack of homogenous data across articles.
3. Lack of clear mortality figures, relating to various ASA grades and genders.
4. Limited number of articles reporting ITU admission data.

7. Conclusions

We found that the higher ASA had a direct relationship with mortality and the male gender. Female gender itself is associated with a higher risk of mortality regardless of ASA grade. Further case control trials and/or randomised case control studies are ideal for determining the gender inequality in mortality for ITU patients as well.

Key summary

The authors have an enormous amount of experience in this field. They utilise NELA scoring system, P-POSSUM and American College of Surgeons Scoring System (ACS) to aid decisions involving emergency laparotomies. However, due to the wide applicability of ASA grades in day-to-day practice and as part of ACS. The authors decided to evaluate if ASA grade alone can predict the outcomes of emergency laparotomy. This is the first time in literature where a hierarchical regression was performed on ASA grades with the dependent variable as mortality. We should give importance to other statuses such as cancer status, malignancies, congenital abnormalities but the ASA system has been prevalent and in practice for a longer time. Therefore, we can only suggest modifying the ASA grade system. The key message is ASA 4 and above are very high-risk models for emergency laparotomy. Therefore, they should all be admitted to ITU for pre- and post-operative care.

Author contribution

Dr. Muzina Akhtar – Joint First Author – Study design, writing.

Dr. Douglas J. Donnachie – Joint First Author – Study design, data collection, data analysis and writing.

Dr. Zohaib Siddiqui – Joint Second Author – Data collection, writing.

Dr. Norman Ali – Joint Second Author – Data collection, writing.

Mr. Mallikarjuna Uppara – Senior Author & corresponding Author – Study design, data analysis and writing.

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Declaration of competing interest

No conflicts of interest.

Appendix A. Supplementary data

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