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Original Article

Is aggressive intravenous fluid prescription the answer to reduce mortality in severe pancreatitis? The FLIP study: Fluid resuscitation in pancreatitis

Julia McGovern[1], Samuel J Tingle[1], Northern Surgical Trainees Research Association (NOSTRA)[2], Stuart Robinson[3], John Moir[3]

[1]Health Education England North East, Newcastle upon Tyne, UK,
[2]Northern Surgical Trainees Research Association (NOSTRA)*,
[3]Department of HPB and Transplant Surgery, Freeman Hospital, Newcastle upon Tyne, UK

Backgrounds/Aims: Acute pancreatitis is an emergency presentation, which can range from mild to life threatening. Intravenous fluids are the cornerstone of management. Although the WATERFALL trial described the optimal fluid rate in mild/moderate pancreatitis, this trial excluded patients with moderate-severe/severe pancreatitis. The aim of this study was to establish clinical practice regarding intravenous fluid administration in acute pancreatitis and assess its effect on mortality.
Methods: Prospective multi-centre audit of patients with acute pancreatitis was conducted. Data were collected regarding intravenous fluid administration within 72 hours of admission. The primary outcome was 30-day mortality. Multivariable logistic regression was used to identify predictors of 30-day mortality.
Results: Those with severe pancreatitis received more fluid; median 5.7 L versus 4 L in 72 hours (p = 0.003). Participants with severe pancreatitis who died within 30 days received a median of 2,750 mL in the first 24 hours, compared to 4,000 mL in those who survived. The following factors were significant predictors of 30-day mortality: age, Glasgow score, C-reactive protein, ischaemic heart disease, and pancreatitis aetiology. Overall, volume of intravenous fluid was not associated with mortality. However, the effect of intravenous fluid volume on mortality differed significantly depending on pancreatitis severity. In severe pancreatitis, increased volume of intravenous fluid was associated with significant reductions in mortality (odds ratio = 0.655; 0.459–0.936; p = 0.020).
Conclusions: In severe pancreatitis, more aggressive fluid prescription was associated with decreased mortality; however, this was not the case in milder disease. Further prospective trials guiding fluid resuscitation in severe pancreatitis are needed, as the impact of fluid on this population appears to differ from that in those with milder disease.

Key Words: Pancreatitis; General surgery; Infusions

INTRODUCTION

Acute pancreatitis is a common condition encountered within emergency general surgery presentations, frequently accounting for acute admissions [1]. Although a large proportion (up to 80%) of patients are classified as having disease, which is mild or moderate in severity, whereby there is an absence of local or systemic complications and symptoms typically settle with conservative measures, in up to 20% of patients, the condition is classified as severe and life threatening [2,3]. Given the potential to rapidly progress to fulminant illness with multiple organ dysfunction, various measures have been implemented in an effort to improve morbidity and mortality in this patient population [4]. This includes efforts to predict disease severity

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Corresponding author: Julia McGovern, MBChb, BsC (Hons)
Health Education England North East (HEENE), Newburn Riverside,
Newcastle upon Tyne, NE15 8NY, England, UK
Tel: +44-191-210-6400, E-mail: Julia.mcgovern1@nhs.net
ORCID: https://orcid.org/0000-0002-1035-4078

*NOSTRA: list of collaborators in Appendix 1. Joint Stuart Robinson, John Moir.

utilizing scoring systems, such as the Glasgow score, whose criteria are displayed in Supplementary Table 1 [5], revised Atlanta Criteria, and APACHE II score, in addition to rationalizing the use of antibiotics, providing aggressive nutritional support, and optimising the timing of intervention for management of necrosis and collections [6].

There is a wealth of evidence to suggest that the management within the first 48–72 hours of an episode of acute pancreatitis heavily influences the disease course, length of stay, and overall morbidity and mortality [7]. It is during this early disease period that optimal resuscitation is essential. However, despite this knowledge, there is little guidance from national associations and poor-quality evidence in the research literature regarding optimal intravenous fluid administration [8].

On review of published recommendations regarding intravenous fluid administration in acute pancreatitis, it was found that the recommendations were vague and unclear. The American Gastroenterology Association published recommendations on the basis of seven randomized controlled trials (RCTs) examining this subject, yet they failed to find high quality evidence, concluding a "conditional recommendation" with regards to judicious goal directed usage [9]. Working party guidelines published in Gut BMJ highlighted more specific guidelines, recommending that fluids should be given intravenously (crystalloid or colloid as required) to maintain urine output > 0.5 mL/kg. However, they also advised frequent measurement of central venous pressure to guide the replacement rate, a form of monitoring that typically requires a higher level of care [10].

Lastly, NICE have published guidelines with respect to the management of pancreatitis; however, when it comes to advice regarding fluid administration, they simply refer to the general principles and protocols for intravenous fluid therapy, rather than specific guidelines related to pancreatitis [11].

The term "goal directed therapy" is often relied upon when referencing optimal fluid administration, whereby intravenous fluids are titrated against various clinical and biochemical targets (heart rate, blood pressure, urine output, urea, and haematocrit) that reflect perfusion. Historically, this mantra has been the cornerstone of sepsis management, with good evidence that it reduces mortality. Given the similarities in physiological upset caused by the systemic inflamatory response syndrome in acute pancreatitis, it would be assumed that the principles of sepsis management apply in a similar way; however, none of the research studies have been able to replicate the same beneficial outcomes in acute pancreatitis as seen in sepsis.

With intravenous fluids ultimately being the cornerstone of management in these patients to replace third space losses, prevent hypovolaemia, and avoid organ hypoperfusion and associated failure, clearer guidance is needed.

Therefore, this study aims to establish current clinical practice within the North East of England regarding the rate of intravenous fluid administration in patients with acute pancreatitis and to assess its effect on patient outcomes. These findings may also help guide best practice and assist in future trial design.

MATERIALS AND METHODS

Data were collected prospectively from all adult patients with acute pancreatitis at nine sites with general surgical units across the North-East of England. Each site collected data over a 60-day period with 30 days of follow-up. Data collection was conducted between November 2020 and February 2021. Adult patients (aged 18 years or over) presenting with acute pancreatitis, as defined by pre-set biochemical parameters or radiological confirmation in accordance with the revised Atlanta classification, were included [7]. Patients with known hepatobiliary malignancy, chronic pancreatitis, or patients on established renal replacement therapy were excluded. Patients were categorised into severe vs. non-severe pancreatitis based on Glasgow score of ≤ 3 (non-severe) or > 3 (severe).

Using the Northern Surgical Trainees Research Association collaborative surgical network, each participating local hospital allocated a principal investigator team consisting of a consultant surgeon, higher surgical trainee, and a number of junior trainees. Data were collected using a standardised Excel spreadsheet and anonymised data were submitted centrally via a secure, password protected website. The Fluid Resuscitation in Pancreatitis (FLIP) Study was an audit of practice, and therefore, formal ethics approval was not sought. Local Caldicott approval was obtained at each participating centre.

Data were collected on intravenous fluid administration within 72 hours of initial presentation to hospital, in addition to patient demographics, disease characteristics, and clinical outcome measures. As this was a pragmatic study of current practice, patients were managed according to their local hospital intravenous fluid protocol. The primary outcome of interest was 30-day mortality with secondary end-points including admission to high dependency unit/intensive care unit, length of stay, radiological necrosis, and organ failure.

Statistical analysis

For continuous data, normality was evaluated using Shapiro-Wilk tests. Results are presented as mean ± standard deviation or median ± interquartile range, depending on normality. Comparison of volume of fluid delivered to various groups was performed using Mann-Whitney U tests, with Bonferroni correction where more than two groups were being compared.

Missing data were dealt with by multiple imputation using the fully conditional specification technique applied to generate five imputed datasets. A full report of missing data is given in Supplementary Table 2.

Binary logistic regression was performed to assess the association between volume of intravenous fluid delivered in the first 72 hours and 30-day mortality. Backward stepwise selection

was performed to identify key variables, which were included in a multivariable model along with volume of intravenous fluid. Results are displayed as odds ratios (ORs) with 95% confidence intervals (CIs).

When constructing these models the following sensitivity analyses were performed: using Glasgow score as a continuous variable, replacing skewed continuous variables with the logarithm of those variables, and using volume of fluid delivered in the first 24 hours. None of these analyses changed the main results.

An identical approach was used to build a multivariable linear regression model to assess the association between intravenous fluid volume and length of stay. Results are displayed as beta values with 95% CIs, where positive values represent increasing length of stay.

For all tests performed, $p < 0.050$ was deemed significant. All analyses were performed in SPSS version 26 (IBM Corp), and figures were generated using R (R Foundation for Statistical Computing).

Table 1. Cohort demographics (n = 254)

Cohort demographic	Value
Age (yr)	62.0 (18.0–96.0)
Sex	
Male	110 (43.3)
Female	144 (56.7)
BMI (kg/m^2)	29.6 ± 7.7
Pancreatitis aetiology	
ETOH	42 (16.6)
Gallstones	112 (44.4)
Hyperlipidaemia	2 (0.8)
Idiopathic	60 (23.8)
Other	33 (13.2)
Post-ERCP	3 (1.2)
History of ischaemic heart disease (n = 201)	
Yes	31 (15.4)
No	170 (84.6)
History of chronic obstructive pulmonary disease (n = 202)	
Yes	21 (10.4)
No	181 (89.6)
History of heart failure (n = 203)	
Yes	18 (8.9)
No	185 (91.1)
Glasgow score (n = 205)	
Non-severe (< 3)	176 (85.9)
Severe (≥ 3)	29 (14.1)
CRP at 48 h	90.0 (0–607)
Fluid collection on imaging (n = 194)	
Yes	47 (24.2)
No	147 (75.8)
Pancreatic necrosis on imaging (n = 194)	
Yes	17 (8.8)
No	177 (91.2)

Categorical data are presented as counts and percentages. Normally distributed continuous data are presented as mean ± standard deviation. Continuous variables found to be non-normal on Shapiro-Wilk test are presented as or median (range).
BMI, body mass index; ERCP, endoscopic retrograde cholangiopancreatography; CRP, C-reactive protein.

RESULTS

Overall, 254 participants admitted to hospital with acute pancreatitis were included, with 11.2% being readmitted during the study period. The most common aetiology was gallstones (44.4%). A total of 29 participants (14.1%) had severe pancreatitis, as determined by a Glasgow prognostic score of ≥ 3. Three patients underwent endoscopic pancreatic necrosectomy. Full demographics and outcomes of the entire cohort are given in Table 1 and 2, respectively. A separate analysis for each aetiology was not performed. Due to incomplete data collection of some secondary outcomes highlighted in Supplementary Table 2, our analysis focused on the clinically relevant outcomes.

Volume of intravenous fluid delivered

Overall, there was large variability in the volume of intravenous fluid delivered in the first 72 hours after admission (Fig. 1A). Median volume was 4 L (range, 0–13.75 L; interquartile range, 2–6 L).

As displayed in Fig. 1B, the majority of intravenous fluid was delivered in the first 24 hours, with significant reductions on Day 2 and Day 3 ($p < 0.001$ for both). Volume of intravenous fluid delivered over the first three days (median and range) were as follows: Day 1 = 2 L (0–10.5 L), Day 2 = 1 L (0–5 L), and Day 3 = 0 L (0–7.5 L).

Those with severe pancreatitis (Glasgow score ≥ 3) received significantly more intravenous fluid within the first 72 hours; median 5.7 L versus 4 L ($p = 0.003$; Fig. 1C). Further analysis revealed that this was driven by increased intravenous fluid delivery in the first 24 hours ($p = 0.001$; Fig. 1D), with no sig-

Table 2. Overall outcomes of the entire cohort (n = 254)

Cohort outcomes	Value
Length of stay (day)	5.0 (0–62.0)
Readmission to hospital (n = 250)	
Yes	28 (11.2)
No	222 (88.8)
30-day mortality	
Dead	19 (7.5)
Alive	235 (92.5)

Categorical data are presented as counts and percentages. Length of stay was non-normal on Shapiro-Wilk test; thus, they are presented as median (range).

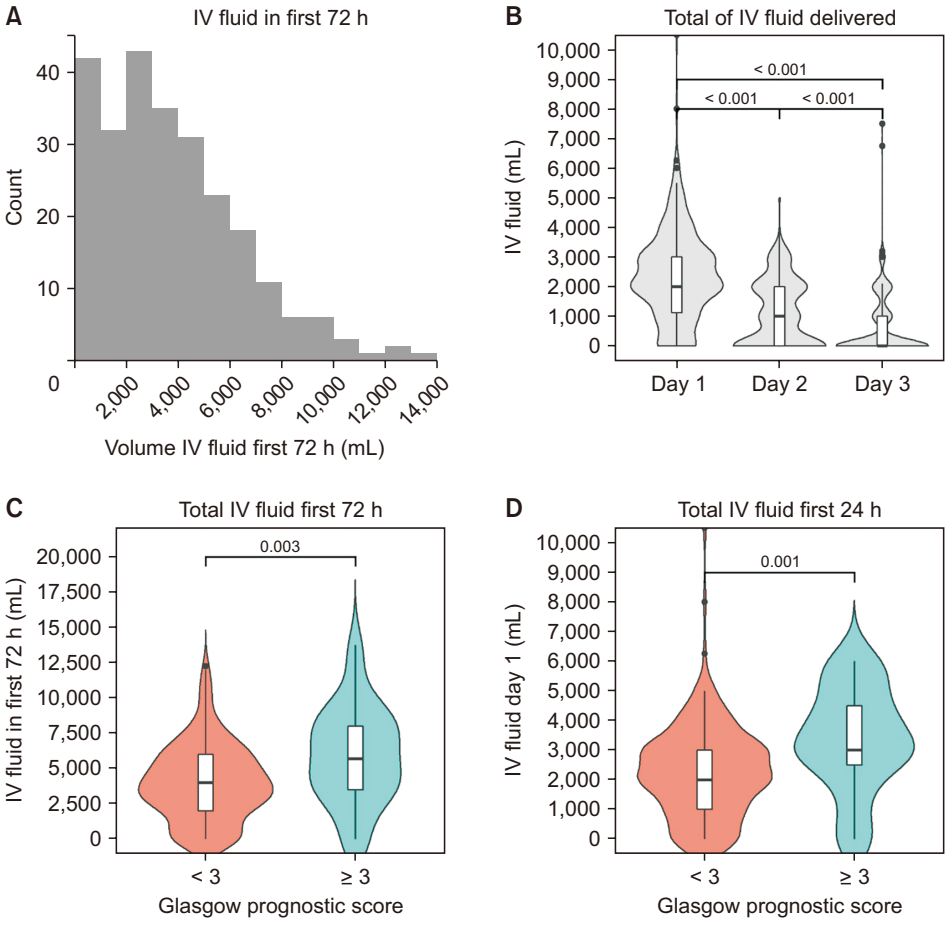

Fig. 1. Volume of intravenous fluid delivered. (A) Histogram displaying total volume of IV fluid delivered in the first 72 hours. (B) Violin and box blots displaying volume of IV fluid delivered on the first, second, and third days of admission. (C, D) Violin and box plots showing volume of IV fluid delivered to patients with non-severe and severe pancreatitis in the first 72 and 24 hours, respectively. Comparisons represent *p*-values from Mann–Whitney U tests. IV, intravenous.

nificant differences between the severe and non-severe groups on Day 2 ($p = 0.275$) or Day 3 ($p = 0.077$).

Comparison of intravenous fluid delivery by mortality

Fig. 2 compares the volume of intravenous fluid given based on whether the participant went on to survive up to 30 days. Overall, there was no difference in the volume of intravenous fluid delivered in patients who were alive or dead at 30 days ($p = 0.922$), a finding which was mirrored when looking at the participants with mild pancreatitis (Fig. 2A, 2B).

However, when looking at the severe pancreatitis subgroup, those who died by 30 days received significantly less intravenous fluid in the first 72 hours that those who survived ($p = 0.005$; Fig. 2C). This effect was driven by differences in intravenous fluid administration within the first 24 hours ($p = 0.033$; Fig. 2D); participants with severe pancreatitis who died within 30 days received a median of 2,750 mL (IQR = 750–3,000 mL) in the first 24 hours, compared to 4,000 mL (3,000–5,000 mL) in those who survived.

Following this, subgroups of participants with ischaemic heart disease and heart failure were evaluated; two conditions that often influence intravenous fluid delivery. Within these subgroups, there was no significant difference in intravenous fluid delivery between those who died and survived (Fig. 2E, 2F), in line with results from the overall cohort.

Assessment of the association between volume of intravenous fluid and mortality

To assess the impact of intravenous fluid delivered in the first 72 hours on 30-day mortality, binary logistic regression was used; univariable analysis suggested no impact (OR = 1.011, 0.857–1.194, $p = 0.895$).

Due to the expectation that patients with increasingly severe disease are more likely to be prescribed intravenous fluid, a multivariable model was built to adjust for confounders. The factors screened for inclusion are shown in Table 3. Variables were selected for inclusion in the multivariable model using backward stepwise selection, and the following factors were retained as significant predictors of mortality: age, pancreatitis severity (Glasgow score), C-reactive protein (CRP) at 48 hours, history of ischaemic heart disease, and pancreatitis aetiology (alcoholic pancreatitis had the highest risk) (Table 3).

Intravenous fluid was not retained as a significant factor on backward stepwise selection, but it was added to the multivari-

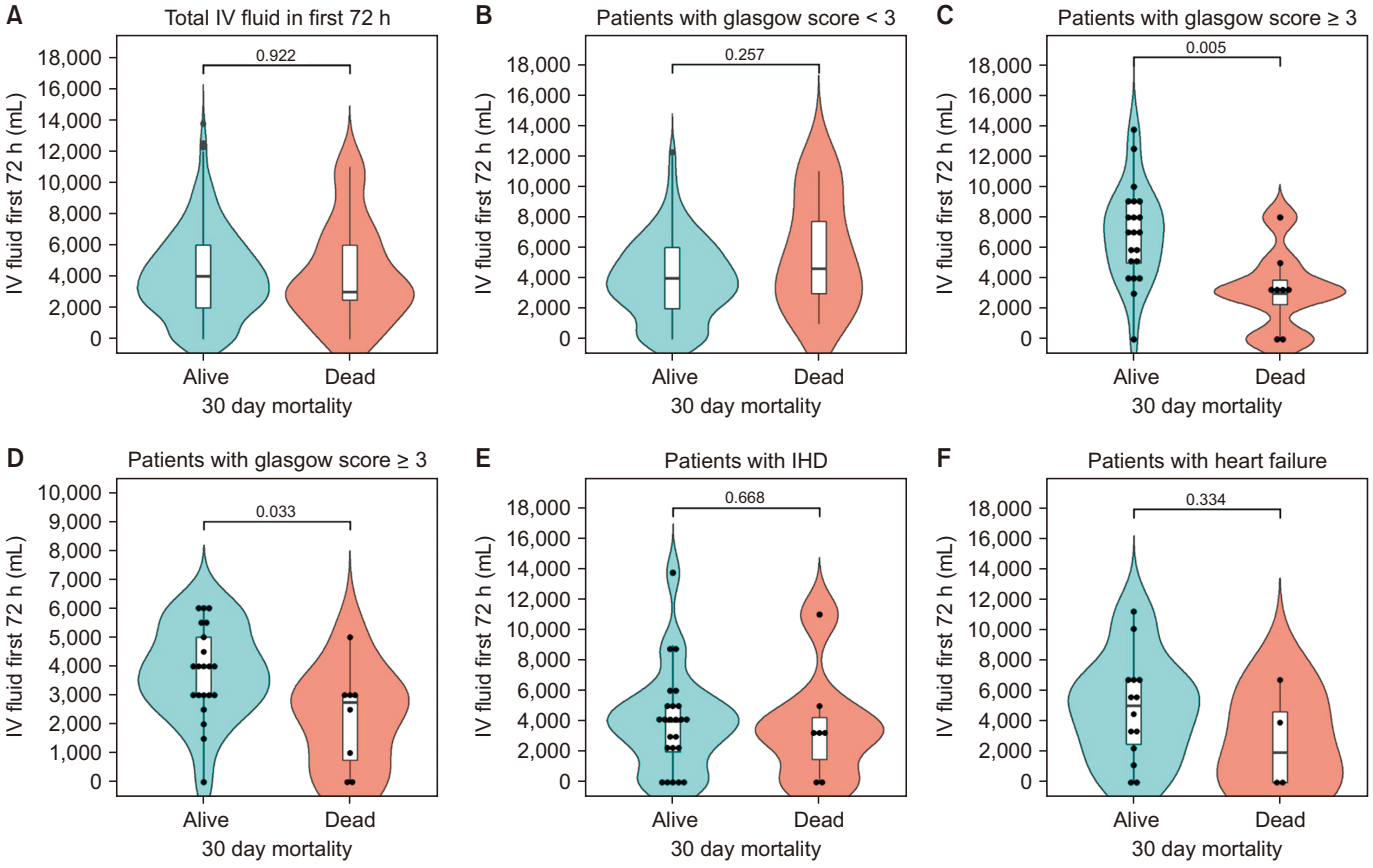

Fig. 2. Volume of intravenous fluid by 30-day mortality displayed with violin and box plots. (A) Entire cohort. (B) Participants with non-severe pancreatitis. (C, D) Participants with severe pancreatitis, showing total IV fluid delivered in 72 and 24 hours, respectively. (E, F) Participants with a history of IHD and heart failure, respectively. Comparisons represent *p*-values from Mann-Whitney U tests. For subgroups with < 50 participants, data for individual participants are presented as a dot plot. IV, intravenous; IHD, ischaemic heart disease.

Table 3. Binary logistic regression for 30-day mortality

	Univariable		Multivariable	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Total fluid first 72 h (L)	1.011 (0.857–1.194)	0.895	0.932 (0.766–1.134)	0.483
Age	1.055 (1.020–1.091)	0.002	1.061 (1.010–1.114)	0.018
Severe pancreatitis (Glasgow score ≥ 3)	9.029 (3.177–25.660)	0.001	4.591 (1.151–18.306)	0.031
CRP at 48 h	1.007 (1.003–1.010)	0.001	1.006 (1.001–1.010)	0.010
History of IHD	5.168 (1.789–14.931)	0.003	4.796 (1.075–21.395)	0.040
Aetiology				
Ethanol	-	-	-	-
Gallstones	0.733 (0.209–2.576)	0.628	0.173 (0.020–1.497)	0.108
Idiopathic	0.675 (0.159–2.863)	0.594	0.192 (0.017–2.193)	0.178
Other	0.796 (0.166–3.810)	0.775	0.438 (0.043–4.415)	0.479
Male sex	1.889 (0.733–4.869)	0.188	-	-
BMI	1.000 (0.892–1.120)	0.997	-	-
Necrosis on imaging	1.958 (0.418–9.171)	0.380	-	-
History of heart failure	3.116 (0.982–9.885)	0.054	-	-
History of COPD	1.441 (0.326–6.371)	0.623	-	-

All variables were screened for inclusion into the multivariable model. Variables were selected for inclusion by backward stepwise selection.
OR, odds ratio; CI, confidence interval; CRP, C-reactive protein; IHD, ischaemic heart disease; BMI, body mass index; COPD, chronic obstructive pulmonary disease; -, not available.

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Table 4. Multiple linear regression for length of hospital stay

	Univariable		Multivariable	
	Beta (95% CI)	*p*-value	Beta (95% CI)	*p*-value
Total fluid first 24 h (L)	0.652 (–0.005, 1.308)	0.052	0.271 (–0.355, 0.897)	0.396
Age	0.059 (0.006, 0.112)	0.029	0.030 (–0.025, 0.085)	0.289
Severe pancreatitis (Glasgow score ≥ 3)	6.621 (3.601, 9.641)	0.001	3.242 (–0.043, 6.527)	0.053
CRP at 48 h	0.026 (0.017, 0.034)	0.001	0.020 (0.011, 0.029)	0.000
Necrosis on imaging	4.328 (–0.074, 8.731)	0.054	4.452 (0.708, 8.196)	0.022
Aetiology				
Ethanol	-	-	-	-
Gallstones	2.210 (–0.733, 5.152)	0.141	-	-
Idiopathic	0.519 (–2.760, 3.798)	0.756	-	-
Other	1.499 (–2.130, 5.128)	0.418	-	-
Male sex	1.854 (–0.199, 3.908)	0.077	-	-
BMI	0.014 (–0.117, 0.146)	0.830	-	-
History of IHD	–0.135 (–2.889, 2.619)	0.923	-	-
History of heart failure	–2.166 (–5.272, 0.941)	0.172	-	-
History of COPD	–0.632 (–3.738, 2.474)	0.689	-	-

All variables were screened for inclusion into the multivariable model. Variables were selected for inclusion by backward stepwise selection.
CI, confidence interval; CRP, C-reactive protein; BMI, body mass index; IHD, ischaemic heart disease; COPD, chronic obstructive pulmonary disease; -, not available.

able model as a key variable of interest. This adjusted analysis confirmed no association between volume of intravenous fluid delivered and 30-day mortality in the overall cohort (adjusted OR = 0.932, 0.766–1.134, $p = 0.483$).

However, in this multivariable model (Table 3), there was significant interaction between volume of intravenous fluid and Glasgow score—the effect of intravenous fluid on mortality differed significantly depending on whether a patient had severe versus non-severe pancreatitis ($p = 0.042$). This prompted a separate analysis including only the cohort with severe pancreatitis (Glasgow score ≥ 3). This analysis revealed a significant reduction in mortality with increasing volumes of intravenous fluid in the severe pancreatitis group (univariable OR = 0.655; 95% CI, 0.459–0.936; $p = 0.020$), which mirrors the findings displayed in Fig. 2C, 2D. The severe pancreatitis subgroup was very small to perform a meaningful multivariable analysis.

Assessment of the association between volume of intravenous fluid and length of stay

To assess the impact of intravenous fluid on length of hospital stay, linear regression was used. A multivariable model (Table 4) was again constructed with included variables selected based on backward stepwise selection. The following variables were retained as predictors of increased length of stay: increasing age, severe pancreatitis (Glasgow Score), CRP at 48 hours, and presence of pancreatic necrosis on imaging. Volume of intravenous fluid delivered had no impact on the length of hospital stay in either univariable or multivariable analysis (Table 4).

DISCUSSION

This study showed significant variations in prescribing IV fluids for patients with acute pancreatitis as well as an associated higher mortality in patients with a Glasgow score of ≥ 3 who receive less IV fluid in the first 72 h of their admission.

Significant variation in the volume of intravenous fluids being delivered over the first 72 hours of admission was likely to be due to the lack of clear published guidance at a regional and national level during the study period. Fluid was consistently given in significantly larger volumes in the first 24 hours of admission, with significantly less fluid being given in the following 48 hours. This was assumed to be due to the fact that patients are typically prescribed a "pancreatitis bundle" of analgesia and fluids on admission, with IV fluids given in the initial period and then they are commonly stopped as oral intake is encouraged and patients work towards discharge if they are clinically well and do not require any intervention. Nonetheless, the variation in practice highlights the absence of knowledge regarding how to safely individualise patient care.

Despite the emphasis on the importance of fluid resuscitation in acute pancreatitis, caveats have been added in the form of warnings against overly aggressive administration. Two RCTs revealed that either hourly rates exceeding 10 mL/kg or haematocrit < 35% within 48 h increased morbidity [12,13], with the American Gastroenterological Association also advising that overly aggressive fluid therapy can be harmful with resultant respiratory compromise or abdominal compartment syndrome [9]. However, in this study, it was found that large volumes of

fluid given to those with mild pancreatitis had no effect on mortality. This finding is supported by a similar study whose cohort was predominantly risk-stratified as having mild disease [14]. However, it is of greater interest that despite there being no overall association between volume of intravenous fluid and mortality in those with severe pancreatitis (Glasgow score ≥ 3), giving more aggressive fluid resuscitation is associated with decreased mortality.

Adding to the argument against aggressive resuscitation, the recently published WATERFALL Trial randomly assigned patients with acute pancreatitis to receive either goal-directed aggressive or moderate fluid resuscitation [15]. This trial found that aggressive fluid resuscitation increased the risk of volume overload, causing harm without any improvement in the primary outcome, which was development of severe pancreatitis during admission. It was concluded that aggressive fluid resuscitation was linked to worse outcomes in critically ill patients. However, this trial excluded patients who were classified as having moderately-severe to severe disease at admission. The FLIP Study adds a new body of evidence, which suggests that the impact of fluid resuscitation strategies differs significantly between those with severe pancreatitis and those with milder disease. Therefore, the findings of the WATERFALL study are likely not generalisable to patients with severe pancreatitis. Further prospective trials are needed to guide fluid resuscitation in those with severe pancreatitis in order to propose a guideline on intravenous fluid administration.

In patients with severe pancreatitis, significantly more fluid was being prescribed in comparison to those with mild/moderate disease and it was typically prescribed in the first 24 h. Those who died had been given significantly less fluid in the first 72 hours of admission. As such, the results suggest that the Glasgow score has an added benefit of identifying those patients who require more IV fluids and more rigorous goal-directed fluid management in the first 72 h of admission. Of note, these results contradict the findings from previously mentioned RCTs [12,13] and a recent meta-analysis published in the World Journal of Gastroenterology [16]. This meta-analysis concluded that early aggressive intravenous fluid therapy (defined as 3–5 mL/kg/h in 24 hours) did not improve mortality, and it reported the potential for increased acute kidney injury and pulmonary oedema. However, these trials failed to risk stratify their patients into severe and non-severe pancreatitis, which may have accounted for their failure to identify improved mortality found in this study, and they concluded that studies are required to investigate subsets of acute pancreatitis, which could benefit from aggressive intravenous therapy.

It is widely accepted practice to risk stratify patients with acute pancreatitis to identify those at risk of developing complications. The basis of this practice is that the triaging of patients within 48–72 hours of presentation allows them to be directed to appropriate levels of care to decrease morbidity and mortality. Although risk stratification is advocated by published guidelines, no single prediction tool has been proven to be the gold standard in practice [17,18]. With a spectrum of severity prediction tools in use in clinical practice, it was found in this cohort that use of the Glasgow-Imrie score was the most prevalent, likely due to the relative simplicity of use. Although the Glasgow score has been criticised as being a poor predictor of pancreatitis severity [19], the fact that it is widely known by junior surgical trainees, who arguably have the maximum influence on the initial volume of intravenous fluid being prescribed, adds to its value in comparison to no severity score being considered. Higher Glasgow scores triggered the clinicians to increase the aggressiveness of their treatment, resulting in significantly higher volumes of intravenous fluids being prescribed. In those with severe disease, more aggressive fluid prescription within 24 hours of admission was associated with improved mortality.

Going forward, this study provides further support towards the need for performing a RCT, specifically looking at the severe pancreatitis patient population, to provide the evidence required to establish if the significant decrease in mortality with increased fluid prescription in patients with severe pancreatitis is causative, and furthermore, establish a recommended fluid regime protocol. Although the study design will be challenging due to the acute nature of disease presentation, the WATERFALL TRIAL has proven that such trials are possible. Alternatively, a cluster trial design, which randomised individual units to specific fluid regimes in appropriate patients, with regimes differing according to volumes given and with volumes administered based on either weight or goal-directed approaches, could be used to ultimately determine the most efficacious and safe approach in this commonly encountered disease and guide best practice.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.14701/ahbps.23.044.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

ORCID

Julia McGovern, https://orcid.org/0000-0002-1035-4078
Samuel J Tingle, https://orcid.org/0000-0001-5529-7815
Stuart Robinson, https://orcid.org/0000-0003-2623-094X
John Moir, https://orcid.org/0000-0002-3161-4713

AUTHOR CONTRIBUTIONS

Conceptualization: JMG, SR, JM. Data curation: All authors. Methodology: All authors. Visualization: JMG, SJT. Writing - original draft: JMG. Writing - review & editing: All authors.

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Appendix 1. Northern Surgical Trainees Research Association (NOSTRA) Collaborative author list

Site key:
Newcastle University Teaching Hospital[1]
James Cook University Hospital[2]
Sunderland Royal Hospital[3]
Darlington Memorial Hospital[4]
University Hospital North Durham[5]
North Tees University Hospital[6]
Northumbria Specialist Emergency Care Hospital[7]
Cumberland Infirmary[8]
Queen Elizabeth Hospital Gateshead[9]

Collaborative authors (alphabetical order):
Hari Avalapati[8]
Khalid Bhatti[3]
Flora Agnes Burns[8]
Sabyasachi Chowdhury[6]
John Corson[3]
Rachel French[5]
Louise Frost[3]
Alex Green[3]
Javaroshini Jegadeeson[7]
Alexander Lloyd[5]
Bertram Marks[9]
Colene McLaughlin[5]
Keshav Nambiar[7]
Chryssa Neo[6]
Ruth Owen[1]
Emmanouil Psaltis[2]
Ellen Ross[4]
Emily Richardson[3]
Elizabeth Seccombe[1]
Keith Seymour[7]
Rachel Sinclair[1]
Shreyas Supparamaniam[5]
Thomas Smyth[4]
Sharmaine Quake[2]
Allison Winarski[4]
John Young[8]

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