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RESEARCH ARTICLE

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Associations between enteral nutrition and outcomes in the SUP-ICU trial: Results of exploratory post hoc analyses

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Abstract

Background: Enteral nutrition may affect risks of gastrointestinal bleeding, pneumonia and mortality in critically ill patients and may also modify the effects of pharmacological stress ulcer prophylaxis. We undertook post hoc analyses of the stress ulcer prophylaxis in the intensive care unit trial to assess for any associations and interactions between enteral nutrition and pantoprazole.

Methods: Extended Cox models with time-varying co-variates and competing events were used to assess potential associations, adjusted for baseline severity of illness. Potential interactions between daily enteral nutrition and allocation to pantoprazole on outcomes were similarly assessed.

Results: Enteral nutrition was associated with lower risk of clinically important gastrointestinal bleeding (cause-specific hazard ratio [HR]: 0.29, 95% confidence interval: [CI] 0.19–0.44, $p < .001$), higher risk of pneumonia (HR: 1.44, 95% CI: 1.14–1.82, $p = .003$), and lower risk of all-cause mortality (HR: 0.22, 95% CI: 0.18–0.27, $p < .001$). Enteral nutrition with allocation to pantoprazole was associated with a

lower risk of mortality (HR: 0.27, 95% CI: 0.21–0.35, $p < .001$), similar to enteral nutrition with allocation to placebo (HR: 0.17, 95% CI: 0.13–0.23, $p < .001$). Allocation to pantoprazole with no enteral nutrition had little effect on mortality (HR: 0.83, 95% CI: 0.63–1.09, $p = .179$), whilst allocation to pantoprazole and receipt of enteral nutrition was mostly compatible with increased all-cause mortality (HR: 1.27, 95% CI: 0.99–1.64, $p = .061$). The test of interaction between enteral nutrition and pantoprazole treatment allocation for all-cause mortality was statistically significant ($p = .024$). **Conclusions:** Enteral nutrition was associated with an increased risk of pneumonia and a reduced risk of gastrointestinal bleeding. The interaction between pantoprazole and enteral nutrition suggesting an increased risk of mortality requires further study.

KEYWORDS

critical illness, enteral feeding, gastrointestinal bleeding, mortality, pneumonia, proton pump inhibitor

Editorial Comment

In this post hoc study of stress ulcer prophylaxis in the intensive care unit (SUP-ICU) trial data, associations and interactions between the provision of enteral nutrition and pantoprazole on the risk of gastrointestinal bleeding, pneumonia, and all-cause mortality were explored. Enteral nutrition was associated with an increased risk of pneumonia and a reduced risk of gastrointestinal bleeding and mortality. Notably, an effect estimate towards increased mortality for the interaction of patients receiving enteral nutrition and pantoprazole may merit further clinical study, but can also support an interpretation that ICU-initiated pantoprazole might be stopped once enteral nutrition is established.

1 | INTRODUCTION

Critically ill patients commonly experience stress-related mucosal damage of the gastrointestinal tract.[1] In some patients, this results in clinically important gastrointestinal bleeding (GIB) events.[1] Clinically important GIB is associated with important patient outcomes such as mortality, along with a considerable medical burden attached to dealing with active GIB events.[2,3] Consequently, strategies to reduce the incidence of GIB have developed. These largely centre on the use of acid suppressants to raise gastric luminal pH, thereby reducing exposure of injured mucosa to low pH states and to endogenous, low pH-dependant proteolytic enzymes.[1,4] This anticipatory pharmacological approach is termed 'stress ulcer prophylaxis' (SUP) and is promoted via international guidelines.[5]

Observational studies have indicated a possible association between the use of enteral nutrition and reduced risk of development of GIB.[6–8] Furthermore, the rapid establishment of enteral nutrition in critically ill patients is widely promoted, potentially making the co-administration of SUP with enteral nutrition a common occurrence.[5,9,10]

The effects of the co-administration of enteral nutrition and SUP on outcomes such as GIB, mortality and pneumonia have been explored in meta-analyses of studies of adult critically ill patients.[11–13] The earliest of these included randomised clinical trials (RCTs) where patients received SUP in the form of histamine 2-receptor antagonists (H2RA).[11] Studies where enteral nutrition was administered to 50% or more of included patients (3 studies, $n = 231$) were compared with studies where less than 50% of participants received enteral nutrition (14 studies, $n = 1605$). The authors concluded that the co-administration of H2RA SUP and enteral nutrition likely increased pneumonia rates and mortality.

More recently, Huang et al. conducted a systematic review with meta-analysis including RCTs where adult critically ill patients received an intervention of any pharmacological SUP (compared with control or placebo) and where the study reported that more than 50% of participants received EN. Seven randomised controlled trials (889 patients) were included. There were no statistically significant differences in bleeding event rates or mortality, but there was a statistically significant increase in pneumonia rates amongst those receiving pharmacological SUP.[12]

The most recent systematic review of predictors of GIB found that enteral nutrition was associated with fewer GIB events when high-risk bias studies were excluded from the analyses, although this was only one study (1077 patients).[13]

In clinical practice, it has previously been reported that 22%–32% of patients have pharmacological SUP discontinued when the patent is enterally fed or is established on full enteral feed,[14,15] although practices may have changed following the results of two large studies[16,17] and weakening of recommendations regarding pharmacological SUP in international guidelines.[5] Some advocate more extensive

discontinuation of pharmacologic SUP in critically ill patients on establishment of enteral nutrition,[18,19] while others advocate continuing when risk factors are present even if enteral nutrition is established.[20] There are also calls for more research and bigger clinical trials.[21]

The stress ulcer prophylaxis in the intensive care unit (SUP-ICU) trial[16] was a large international, blinded RCT comparing the effects of prophylactic intravenous pantoprazole with placebo on outcomes such as mortality, clinically important GIB, and pneumonia in adult ICU patients at risk of GIB. Amongst the daily data captured was information on the administration of enteral nutrition.

We conducted exploratory, post hoc analyses of the SUP-ICU trial to evaluate associations between enteral nutrition and GIB, and to investigate if the use of enteral nutrition modified any such associations between pharmacologic SUP and patient outcomes and vice versa. Our hypotheses were that enteral nutrition would be associated with less GIB, minimal associations with mortality, and increased occurrence of pneumonia.

2 | METHODS

2.1 | Design and setting

The study was conducted according to a protocol and statistical analysis plan written and published after the SUP-ICU trial results were published, but before any of the analyses reported herein were conducted.[22] We included 3291 patients from 33 ICUs in 6 countries enrolled in the SUP-ICU trial in the analyses.

2.2 | Outcomes and definitions

The research questions were:

1. '*Is there an association between the use of enteral nutrition and GI bleeding, all-cause mortality, or pneumonia in critically ill patients, when accounting for the use of SUP?*'
2. '*Are potential associations of use of enteral nutrition modified by SUP with pantoprazole and vice versa in critically ill patients?*'

The primary outcome was clinically important GIB in ICU within 90 days, with secondary outcomes being pneumonia in ICU within 90 days, and all-cause mortality within 90 days.

Definitions for overt GIB, clinically important GIB, pneumonia, and mortality were as described in the SUP-ICU trial[16] and are presented in the Supporting Information Material. Any enteral nutrition was defined as receipt of any dose of enteral feeding, including oral nutritional intake, during the day. Sustained enteral nutrition was defined as the receipt of enteral nutrition on 2 consecutive days. Allocation to enteral nutrition status (no enteral nutrition, enteral nutrition, or sustained enteral nutrition) was not randomised. Since patients could move from one status to another, enteral nutrition status was analysed as a time-varying variable.

2.3 | Statistics

Statistical analyses were conducted using R v. 4.2.1. Two-tailed $p < .05$ were considered statistically significant with 95% confidence intervals (CIs) presented; however, all findings are interpreted in terms of compatibility while being considered exploratory and interpreted with caution.[23]

2.4 | Descriptive data

Descriptive baseline demographic and outcome data are presented as medians with interquartile ranges (IQRs) for continuous variables and counts with percentages for categorical variables, stratified by the combination of treatment allocation and whether patients received enteral nutrition on the first study day.

2.5 | Assessment of associations and potential interactions

When considering variables such as receipt of enteral nutrition, participants may change status (e.g., a participant may initially not receive enteral nutrition, and then after a few days begin to receive enteral nutrition and so change status). Therefore, potential associations between enteral nutrition and outcomes were assessed using extended Cox models with time-varying co-variates[24] and competing events.[25] Models included enteral nutrition use as a time-varying co-variate and treatment allocation, with adjustment for baseline Simplified Acute Physiology Score (SAPS) II[26] to account for severity of illness. Mortality, clinically important GIB, or ICU discharge were considered as competing events with observations censored at the first competing event.

An assessment for potential interaction between enteral nutrition and SUP was made using a similar model including interaction terms between enteral nutrition (time-varying) and treatment allocation.

2.6 | Assessment of model adequacy

We conducted several assessments of the validity of the statistical models used and applied appropriate handling or supplementary models where necessary (Supporting Information Material).[27]

Additional details on the assessment of model adequacy and handling of violations of the model assumptions are presented in the Supporting Information Material.

2.7 | Sensitivity analyses

The primary analyses included enteral nutrition as a time-varying covariate; pre-planned sensitivity analyses included sustained enteral nutrition instead.[22] Furthermore, the analyses with clinically important

GIB as the outcome were supplemented with pre-planned sensitivity analyses with overt GIB as the outcome.[22] Practices with respect to initiation of enteral nutrition may vary by country. Admission type may also affect enteral nutrition practices. Thus, further post hoc sensitivity analyses were undertaken to adjust for these variables (country and medical vs. surgical admission). Finally, we considered that clinically important GIB may typically lead to treatment changes (i.e., placebo or SUP would be replaced with therapeutic proton pump inhibitor [PPI] and so may affect mortality). Thus, post hoc sensitivity analyses of the models with mortality as the outcome but without considering clinically important GIB as a competing event were also undertaken.

2.8 | Missing data handling

The amount of missing data for each variable is presented. As we knew that 7.6% of the SAPS II values were missing,[16] analyses were conducted using multiple imputed datasets as planned.[22] Further details, including a description of the imputation procedure, are presented in the Supporting Information Material.

3 | RESULTS

We included a total of 3291 patients in the analyses. The median (IQR) age was 67 (56–75), and 2106 (64.0%) were males. The baseline characteristics and descriptive outcome data of the SUP-ICU cohort stratified by treatment allocation and enteral nutrition on Day 1 are displayed in Table 1.

The total number of events occurring in 3291 patients before censoring for any reason (i.e., loss-to-follow-up or competing events) were 100 clinically important GIB events, 221 overt GIB events, 490 pneumonia events and 446 mortality events.

The associations between enteral nutrition and sustained enteral nutrition, and the outcomes of interest, including interactions with SUP, are presented in Figures 1 and 2.

The adjusted hazard ratios (HR) by SUP treatment allocation and enteral nutrition status for each outcome are displayed as forest plots in the top panels; pantoprazole (vs. placebo) and enteral nutrition (vs. no enteral nutrition) in Figure 1, or sustained enteral nutrition (vs. no sustained enteral nutrition) in Figure 2. The bottom panels in both figures display results from models with interactions between treatment allocation and enteral nutrition status and the overall p value for the interaction test (indicated by *). Exposure to enteral nutrition was statistically significantly associated with a lower cause-specific HR for both clinically important GIB and overt GIB (HR: 0.29, 95% CI: 0.19–0.44, $p < .001$ and HR: 0.33, 95% CI: 0.25–0.44, $p < .001$, respectively). The risk of clinically important and overt GIB events was also statistically significantly lower in patients randomised to pantoprazole (HR: 0.64, 95% CI: 0.43–0.96, $p = .028$ and HR: 0.58, 95% CI: 0.44–0.76, $p < .001$, respectively). The tests of interaction between exposure to enteral nutrition and SUP treatment allocation for both clinically important and overt GIB were not statistically significant ($p = .132$; $p = .848$, respectively).

Overall, exposure to enteral nutrition was statistically significantly associated with a greater cause-specific HR for pneumonia (HR: 1.44, 95% CI: 1.14–1.82, $p = .003$) (Figure 1). Figure 3 shows the results of the supplementary model for pneumonia with the binary time transformation at 4 days (median pantoprazole treatment time), that is, the estimated associations on Days 1–4 and Days 5 or later, which are largely consistent with the main results.

The HRs for all-cause mortality in patients exposed to enteral nutrition or sustained enteral nutrition were statistically significantly reduced (HR: 0.22, 95% CI: 0.18–0.27, $p < .001$ and HR: 0.35, 95% CI: 0.28–0.43, $p < .001$), with no statistically significant difference in patients randomised to SUP with pantoprazole (HR: 1.05, 95% CI: 0.87–1.26, $p = .631$ and HR: 1.06, 95% CI: 0.88–1.28, $p = .542$).

Exposure to pantoprazole with enteral nutrition was mostly compatible with an increase in all-cause mortality, although this was not statistically significant (HR: 1.27, 95% CI: 0.99–1.64, $p = .061$). Similar results were seen in patients receiving pantoprazole and sustained enteral nutrition (HR: 1.3, 95% CI: 1.00–1.69, $p = .051$). There was a statistically significant interaction for all-cause mortality between pantoprazole and enteral nutrition ($p = .024$) and pantoprazole and sustained enteral nutrition ($p = .030$) (Figures 1 and 2).

The results of additional post hoc sensitivity analyses of the models with mortality as the outcome but without considering clinically important GIB as a competing event, and also analyses that adjusted for country and for admission type were similar to those from the primary analyses (Figures S1 and S2; Tables S1 and S2 Supporting Information Material).

4 | DISCUSSION

In this post hoc exploratory study of the SUP-ICU trial, we observed that enteral nutrition and allocation to pantoprazole were both associated with reduced risk of GIB. Furthermore, enteral nutrition was associated with an increased risk of pneumonia, most pronounced in patients allocated to placebo rather than pantoprazole. Finally, there was an associated reduction in all-cause mortality with enteral nutrition, however, all-cause mortality was increased in patients receiving both enteral nutrition and pantoprazole with interaction between receipt of enteral nutrition and pantoprazole shown in the statistical model.

The use of pharmacological stress ulcer prophylaxis with PPIs has been clearly shown to reduce GIB in two large trials.[16,17] The use of enteral nutrition to reduce GIB is debated, and in practice, a variety of approaches are used, perhaps reflecting uncertainty in the available evidence.[14,15,20] Our data show an association between the use of enteral nutrition and reduced rates of GIB. However, the use of enteral nutrition was not randomised, so it is possible that enteral nutrition was only provided to less sick patients. Despite adjusting for the severity of illness in the analyses, residual confounding, including confounding by indication, may remain.

TABLE 1 Baseline and outcome variables stratified by presence or absence of enteral nutrition on Day 1, and treatment allocation (pantoprazole stress ulcer prophylaxis or matching placebo) in 3291 critically ill patients.

	Enteral nutrition		No enteral nutrition	
	Pantoprazole ($n = 956$)	Placebo ($n = 929$)	Pantoprazole ($n = 688$)	Placebo ($n = 718$)
Median age (IQR), years	67.0 (56.0–75.0)	67.0 (55.0–75.0)	68.0 (56.8–76.0)	67.5 (55.0–75.0)
Male sex, number (%)	578 (60.5%)	591 (63.6%)	461 (67.0%)	476 (66.3%)
Coexisting conditions, number (%)				
Chronic lung disease	219 (22.9%)	177 (19.1%)	132 (19.2%)	129 (18.0%)
Previous myocardial infarction	86 (9.0%)	76 (8.2%)	70 (10.2%)	66 (9.2%)
Chronic heart failure	53 (5.5%)	71 (7.6%)	47 (6.8%)	28 (3.9%)
Immunosuppression	24 (2.5%)	17 (1.8%)	11 (1.6%)	10 (1.4%)
Haematological malignancy	43 (4.5%)	29 (3.1%)	21 (3.1%)	26 (3.6%)
Metastatic cancer	27 (2.8%)	29 (3.1%)	29 (4.2%)	26 (3.6%)
AIDS	3 (0.3%)	1 (0.1%)	3 (0.4%)	0 (0.0%)
Chronic liver disease	28 (2.9%)	30 (3.2%)	17 (2.5%)	19 (2.6%)
Chronic renal replacement therapy	10 (1.0%)	12 (1.3%)	10 (1.5%)	5 (0.7%)
Coagulopathy	202 (21.1%)	149 (16.0%)	150 (21.8%)	150 (20.9%)
Pharmacological risks, number (%)				
Use of anticoagulants	315 (32.9%)	291 (31.3%)	198 (28.8%)	193 (26.9%)
Use of NSAIDs or ASA	155 (16.2%)	142 (15.3%)	123 (17.9%)	113 (15.7%)
Use of IV thrombolysis	15 (1.6%)	11 (1.2%)	10 (1.5%)	11 (1.5%)
Admitted to university hospital, number (%)	681 (71.2%)	652 (70.2%)	502 (73.0%)	537 (74.8%)
Median time from ICU admission to randomisation (IQR), h	19.0 (9.8–39.0)	20.0 (10.0–37.0)	10.0 (3.0–18.0)	9.0 (4.0–17.0)
Admission type, number (%)				
Medical	662 (69.2%)	638 (68.7%)	384 (55.8%)	359 (50.0%)
Emergency surgery	232 (24.3%)	233 (25.1%)	258 (37.5%)	325 (45.3%)
Elective surgery	62 (6.5%)	58 (6.2%)	46 (6.7%)	34 (4.7%)
Use of invasive mechanical ventilation, number (%)	746 (78.0%)	759 (81.7%)	527 (76.6%)	557 (77.6%)
Use of vasopressors or inotropes, number (%)	646 (67.6%)	602 (64.8%)	457 (66.4%)	491 (68.4%)
Use of renal replacement therapy, number (%)	80 (8.4%)	54 (5.8%)	43 (6.2%)	45 (6.3%)
Median SAPS II (IQR)	48.0 (38.0–58.0)	47.0 (37.0–58.0)	50.0 (40.0–61.0)	50.0 (38.0–61.0)
Clinically important GIB, number (%)	18 (1.9%)	32 (3.4%)	23 (3.3%)	37 (5.2%)
Overt GIB, number (%)	42 (4.4%)	58 (6.2%)	46 (6.7%)	90 (12.5%)
Pneumonia, number (%)	162 (16.9%)	176 (18.9%)	104 (15.1%)	90 (12.5%)
Mortality, number (%)	290 (30.3%)	279 (30.2%)	220 (32.1%)	220 (30.8%)

Note: There were missing values for median SAPS II (249, 7.6%), median SOFA score (193, 5.9%) and mortality (9, 0.3%). There were no other missing values.

Abbreviations: AIDS, acquired immune deficiency syndrome; ASA, acetylsalicylic acid; GIB, gastrointestinal bleeding; ICU, intensive care unit; IV, intravenous; NSAID, nonsteroidal anti-inflammatory drug; SAPS II, Simplified Acute Physiology Score II.

Pneumonia has long been considered a potential risk factor when using acid-suppressing medications for SUP and is commonly measured as a potentially serious adverse event in trials.[16,28–32] Overall, we found allocation to pantoprazole had a neutral or uncertain effect on pneumonia risk, whilst exposure to enteral nutrition was associated with an increased risk.

The use of a binary time cut-off in the model that compared pneumonia rates before and after the median pantoprazole treatment time (4 days) was used to investigate the stability of the outcome with time, yielding similar results to the main analysis. Pantoprazole has a short plasma half-life (approximately 1.1 h),[33] and is only available to irreversibly bind with actively secreting proton pumps for a few hours. In PPI naïve patients, dormant proton pumps are left unaffected and can cycle through to become active a few hours later, leading to a delay before gastric pH is consistently raised throughout the day.[34] If pneumonia is facilitated by bacterial growth in the oesophagus and stomach in a pH-neutral environment, then it may be some time before these conditions are achieved, with a subsequent delayed

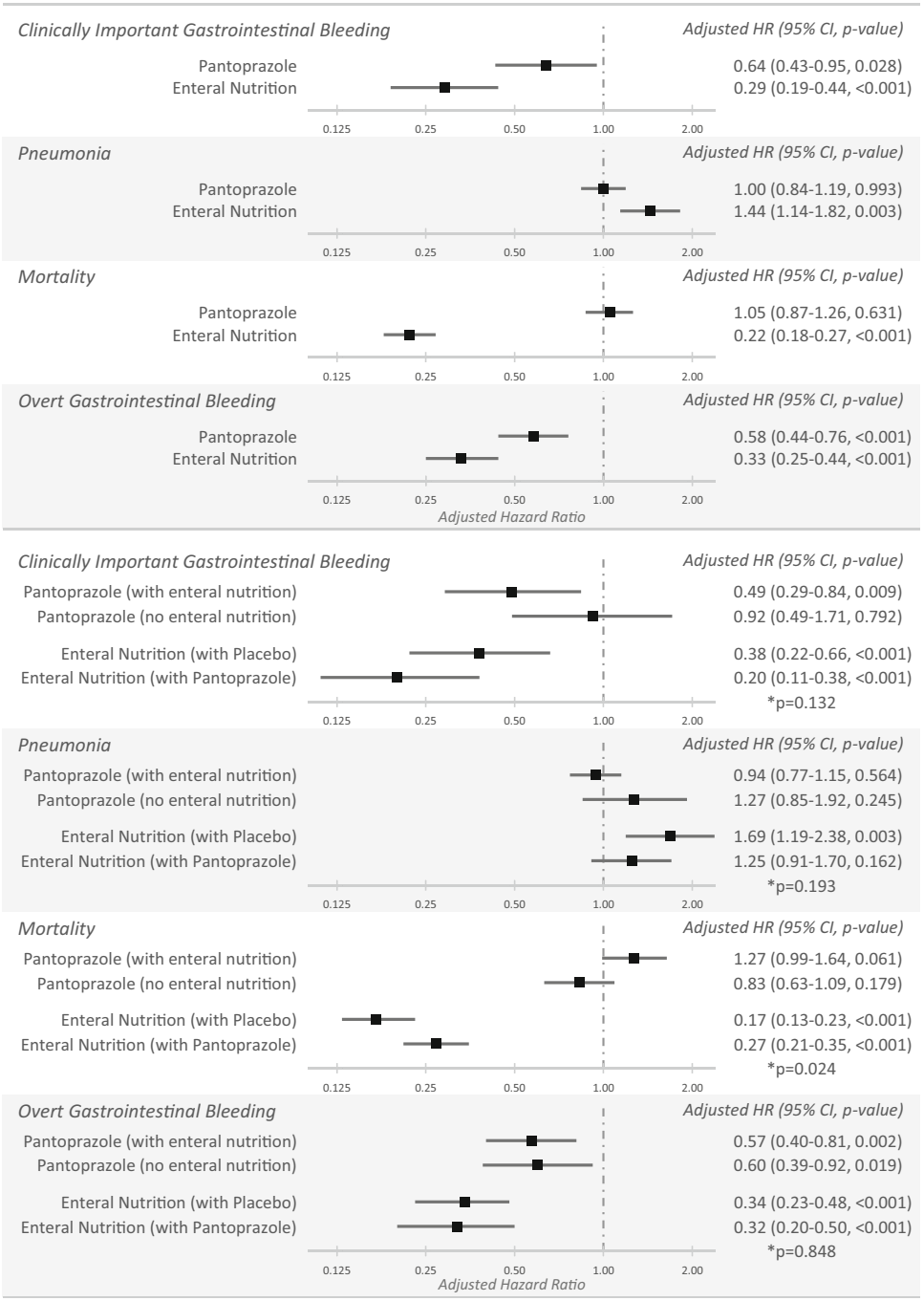

FIGURE 1 Forest plots of associations between enteral nutrition and stress ulcer prophylaxis with pantoprazole for clinically important gastrointestinal bleeding (GIB), pneumonia, all-cause mortality, and overt GIB. The top panels display results by group allocation (pantoprazole vs. placebo) and enteral nutrition status, the bottom panel displays results from models with interactions between treatment allocation and enteral nutrition status. *Test of interaction between enteral nutrition status and pantoprazole treatment allocation.

effect on rates of nosocomial pneumonia development secondary to acid suppression. Patients were excluded from SUP-ICU if they had a requirement for ongoing daily treatment with acid suppressants after ICU admission, meaning participants were mostly PPI naïve.[16]

Overall, enteral nutrition exposure was associated with reduced mortality and a non-statistically significant increase in mortality in patients randomised to pantoprazole. There is active debate regarding mortality signals with PPI as SUP, with various analyses of large trials and systematic reviews adding information[35–38] and further work ongoing to add more information[32]; the association between enteral nutrition and mortality may be due to confounding by indication.

A systematic review in 2010[11] concluded that SUP (H2RA) and feeding might lead to harm, as evidenced by an increase in hospital mortality, although only 3 of the 17 studies were allocated to the enteral nutrition group. Another review included PPIs, H2RA or sucralfate as SUP in seven trials where the majority of patients received enteral nutrition and found no effect on mortality of SUP.[12] Our data indicate that the associated mortality risk is greatest in patients randomised to pantoprazole and receiving enteral nutrition, with a statistically significant interaction between these variables in the model. Because receipt of enteral nutrition was not randomised, this finding is hypothesis generating only.

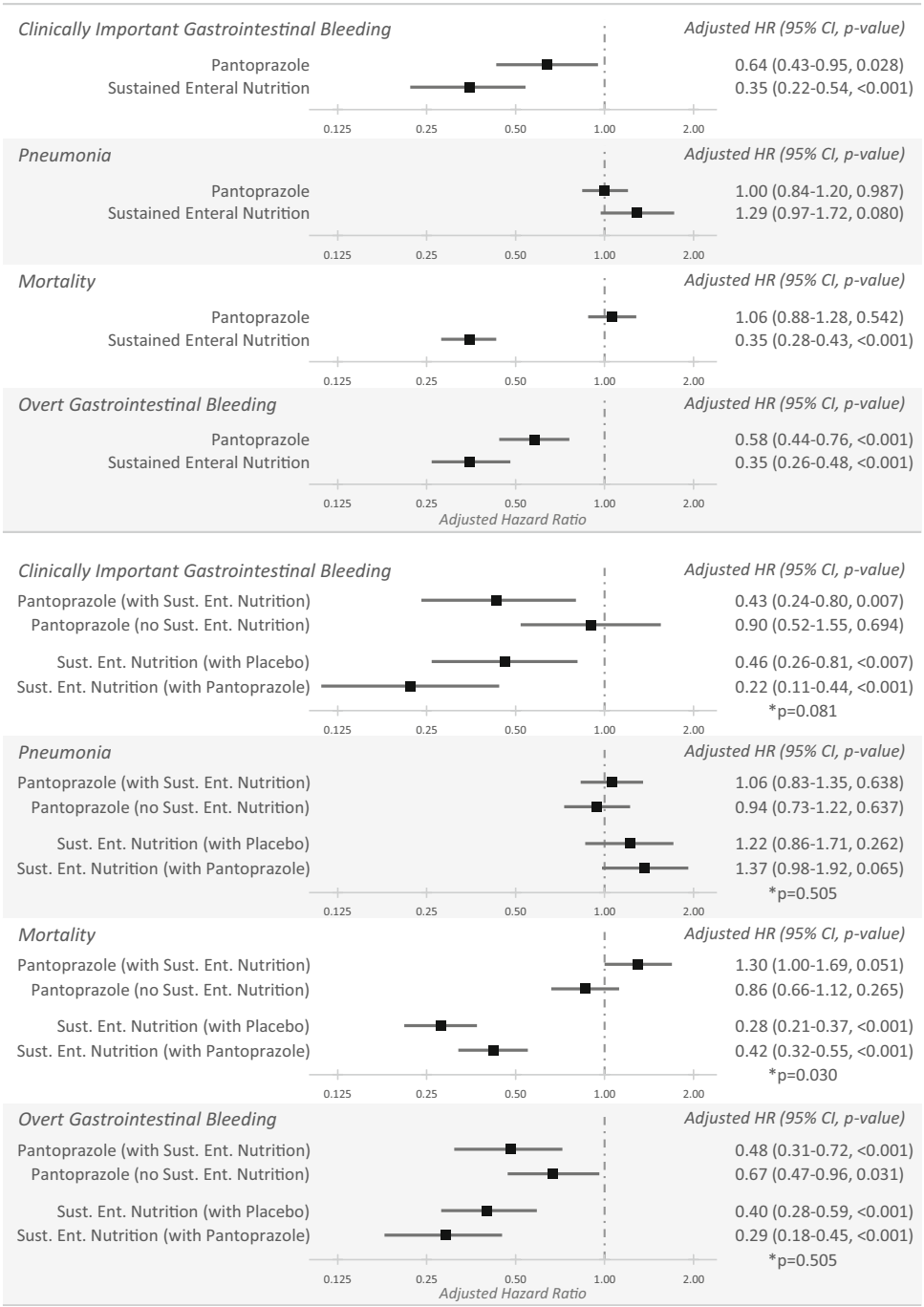

FIGURE 2 Forest plot of associations between sustained enteral nutrition (Sust. Ent. Nutrition) and stress ulcer prophylaxis with pantoprazole for clinically important gastrointestinal bleeding (GIB), pneumonia, all-cause mortality, and overt GIB. The top panels display results by group allocation (pantoprazole vs. placebo) and Sust. Ent. Nutrition status, the bottom panels display results from models with interactions between treatment allocation and enteral nutrition status. *Test of interaction between Sust. Ent. Nutrition status and pantoprazole treatment allocation.

We did not specifically explore differences in outcomes between patients fed earlier versus later. In SUP-ICU, 57.2% of patients began receiving enteral nutrition 1 day, rising to 74.8% within 2 days of enrolment.[16] Recent data suggest that less aggressive feeding administered early in shock states leads to better patient outcomes than standard feeding regimens.[39] Some have implicated inhibition of autophagy through higher feed rates as a mechanism that produces harm.[40] Autophagy is an adaptive survival process induced in states of physiological stress.[41] The potential for an important role of autophagy as a facet of nutrition status in critical illness has been recently summarised.[42] Enhancement of autophagy is implicated as a survival mechanism for some cancers when exposed to chemotherapeutic agents[43,44] the use of PPIs has been explored as adjunctive therapy to inhibit autophagy and thereby reduce cancer cell survival.[43,45–48] It is tempting to speculate on the potential for both nutrition and pantoprazole to inhibit autophagy as a possible explanation for the significant interaction between enteral nutrition and PPI seen with respect to mortality, and as a potential mechanism contributing to a trend towards increased mortality in sicker patients allocated to pantoprazole in SUP-ICU.[16]

A strength of this study is the use of a comprehensive dataset collected from a large RCT that had low levels of missing data and wide generalisability. The quantity of nutrition administered was not recorded, so we also analysed sustained enteral nutrition as a

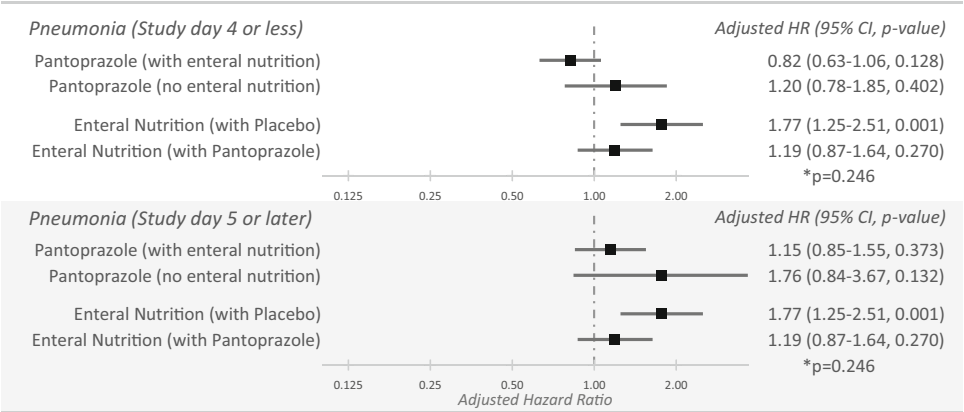

FIGURE 3 Pneumonia, time-varying effects: hazard ratios for pneumonia by group by time (median SUP treatment time 4 days). *Test of interaction between enteral nutrition status and pantoprazole treatment allocation.

sensitivity analysis. There may also be unmeasured confounders, for example, pantoprazole could reduce the volume of gastric secretions, and since gastric residual volume information may be used to guide initiation and titration of enteral nutrition, allocation to pantoprazole may affect the timing of enteral nutrition initiation when compared with placebo. Certain patient characteristics could affect the clinical use of enteral nutrition, patients with gastrointestinal surgery, for example, may be more likely to be initially represented in the no enteral nutrition group. Since exposure to enteral nutrition was not randomised, our findings are best described as associations with further work required to confirm them. This would require a major trial, along with an acceptable way to handle randomisation of enteral nutrition that meets the requirements of equipoise.

In the absence of such a trial, and in light of the associations seen in our results, it seems sensible to consider ceasing newly initiated SUP with pantoprazole when patients are commenced on enteral nutrition until the results of further studies are known.

5 | CONCLUSIONS

The provision of enteral nutrition to ICU patients is associated with an increased risk of pneumonia and reduced GIB. An interaction between pantoprazole and enteral nutrition that suggests an increased mortality risk requires further study.

AUTHOR CONTRIBUTIONS

MB, AG, TL and MHM contributed to the conceptualisation and design of this study. MB, AG and MHM were responsible for the writing of the original draft and decision to submit for publication. AG performed the statistical analyses with supervision from TL. MHM provided overall supervision. All authors contributed to the critical revision and writing of the publication, and for the final approval to submit including accountability for the accuracy and integrity of the publication.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request (requests reviewed by the SUP-ICU Steering Committee).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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