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Temperature, Neutrophils and Multiple Organ Failure Score: A Simple Scoring System to Predict Mortality Following Perforated Peptic Ulcer

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ABSTRACT

Purposes: Patients with perforated peptic ulcer (PPU) present with signs of sepsis and appropriate management can be offered to achieve an optimal outcome of disease. We propose evaluating the severity of intra-abdominal sepsis in case of PPU with a new score called TNM, name borrowed by cancer staging, with the aim of assess its predictive value.
Methods: We included 183 patients with diagnosis of complicated PPU. We defined categories T (Temperature), N (Neutrophils count) and M (MOF); then, patients were grouped in stages (0-IV). Variables analysed were age, sex, ASA, blood transfusion, causes of sepsis, temperature, neutrophils count, preoperative organ failure, immune-compromised status, stage (0-IV).
Results: Patients were grouped as follows: none at stage 0; 6 at stage I; 72 at stage II, 72 at stage III; 33 at stage IV. ASA score, neutrophils count, preoperative organ failure, stage III-IV emerged as statistically significant different prognostic factors. ASA score and stage were significant independent predictors of post-operative mortality in multivariate analysis.
Conclusion: Our proposed system could define and help to assess the mortality risk.
Key words: peptic ulcer, perforated peptic ulcer, intra-abdominal sepsis, localized peritonitis, generalized peritonitis, scoring systems

INTRODUCTION

Peptic ulcer disease, both duodenal and gastric, despite the widespread availability of effective acid reduction agents and antibiotic therapy for Helicobacter pylori (1), is associated with potentially life-threatening complications, including bleeding, perforation, penetration and obstruction. Intra-abdominal sepsis (IAS) after perforation is the second most frequent complication after bleeding (2,3). A high risk for morbidity (20-50%) and mortality (1.3-40%) is encountered in surgically treated perforated peptic ulcer (PPU)

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patients (4-9). Patients with PPU present with signs of sepsis and by a careful preoperative assessment of the patients' severity grade, appropriate management can be offered to achieve an optimal outcome of disease (10,11). Many scoring systems (Boey score, Peptic Ulcer Perforated (PULP) Score, American Society of Anaesthesiologists (ASA) score) have been proposed to predict mortality after PPU (12-14). PULP score seems to be the most reliable, but it is very complex to use (12). Boey score is easier but its predictability value is not consistent (12,15-17). ASA score is a general surgical risk score not intended for PPU patients in particular, and its major drawback is its subjective assessment (12,15). Nowadays, in the clinical practice the grading systems are not always employed for PPU, although they seem to give precise clinical indications, because some of them are too complicated (PULP score) and others are too aspecific (ASA score). In our work, we tried to assess the severity of IAS as a complication of PPU using a new TNM score: T indicates Temperature, N Neutrophil count and M Multiple organ failure (MOF) (18,19). In this study we aimed to evaluate significance of this score to predict mortality of patients with complicated PPU.

MATERIALS AND METHODS

The TNM system was studied in 183 patients with complicated PPU and IAS, managed in General Surgery and Hepato-biliopancreatic Surgery at our Department of Surgery in the period between April 2012 and December 2019. Pregnant women, patients aged < 18, immune-compromised patients and those who underwent laparoscopic surgery were excluded.

At the presentation, patients were clinically evaluated; blood tests and imaging exams were performed. Intravenous antibiotic therapy was set up: Ciprofloxacin 200 mg or Amoxicillin-clavulanic 2 gr and Metronidazole 500 mg.

The anthropometric data were collected in an electronic database. According to clinical and laboratory characteristics, the patients were classified based on our system. *Table 1* resumes the definitions. The classes of the patients is showed in *table 2*, which also shows the groupings in stages (stage 0-IV).

For the study of this system, we used retrospective data of 102 patients between January 2001 and January 2012 (control group); the study group was prospectively evaluated. TNM stage was firstly evaluated at the time of the presentation and then every day of recovery. The primary endpoint was to assess the efficacy of TNM score in forecasting mortality at 30 days. The work has been reported in line with the STROCSS criteria (20).

Table 1 - Definition of organ failure

Renal	One or more the following :
	• Dialysis • Creatinine > 1.4 mg% • Urine output < 150 ml per 8 h
Respiratory	pO_2 < 60 mmHg
Cardiovascular	One or more the following:
	• Hypotension ≤ 90 mmHg • Use of inotropic support : - Dopamine - Dobutamine - Epinephrine - Norepinephrine

Statistical analysis

The characteristics of the study sample were analysed with descriptive statistics; the discrete and nominal variables were expressed using frequencies and percentages; for continuous variables, medians and range were reported. The frequency distribution of prognostic factors (age classes, sex, ASA score, blood transfusion, causes of sepsis, fever, neutrophil count, pre-operative organ failure, immuno-compromised status, TNM stage) were examined between outcome groups (alive or dead). Chi square (χ^2) test was used to analyse statistical differences. Variables significantly different between the two groups were introduced in the multivariate logistic model to obtain independent predictors of death, with associations reported as odds ratios (ORs) and 95% confidence intervals (CIs).

Model discrimination was evaluated using the receiver operating characteristics (ROC) curve. All data were electronically recorded; statistical analyses were performed using the Stata Statistical Software (Release 15/IC, College Station, TX: Stata Corp LP). All the tests were two-tailed, and $p < 0.05$ was considered statistically significant.

RESULTS

One hundred eighty-three consecutive patients were included; they had a mean age of 67.0 years (range 23 to 86). No significative differences of age between the sexes was reported. One hundred and seventeen patients (63.9%) were diagnosed with localized peritonitis or abscesses and sixty-six (36%) with generalized peritonitis. Distribution of patients into the stages, according to clinical findings and laboratory values, is showed in *table 3*. Death occurred

Table 2 - Temperature- Neutrophil- Multiple organ failure (TNM) Staging System for complicated IAS* after PPU**

TNM score		
Temperature (T) * **	**Maximum daily temperature (°C) ******	
T0	36.4- 37.4	
T1	37.5-38.4	
T2	38.5-39.0	
T3	39.1- 39.5	
T4	>39.5 ; <36.4	
Neutrophil (N)	**%**	
N0	40-74	
N1	75-85	
N2	86-90	
N3	> 90 ; < 40	
Multiple organ failure (M)	**Organ failure**	
M0	No organ failure	
M1	One organ failure	
M2	Two or more organ failure	
Stage	**TNM**	**Clinical Profile**
0	T0 N0 M0	Mild Sepsis
I		Mild Sepsis
Ia	T1; N0, N1; M0	
Ib	T2; N0, N1; M0	
II		Moderate Sepsis
IIa	T3; N0,N1,N2; M0	
IIb	T4; N0, N1, N2; M0	
III		Severe Sepsis
IIIa	any T; N3; M0	
IIIb	any T; any N; M1	
IV	any T; any N; M2	Septic Shock

* IAS : Intra-Abdominal Sepsis, **PPU: Perforated Peptic Ulcer, ***Oral temperature,
****Temperature should be recorded at least 4 times in 24h

in 31.2% patients, and their mean age was 59.7 years (range 23 – 74). The mean age of survivors was 66.1 years (range 45 – 86). No patient in the stage I died; mortality progressively increased among stages and reached 52.6% at the stage IV (*table 3*).

Statistically significant differences using χ^2 test emerged for ASA score, neutrophil count, pre-operative organ failure and TNM stage between outcome groups (*table 4*). As neutrophil count and pre-operative organ failure are variables that define the TNM stage, they

Table 3 - IAS* after PPU: Stage TNM on the day of diagnosis/admission and mortality**

Stage TNM	**N° (%)**	**Dead N ° (%)**	**Alive N ° (%)**	**Clinical Profile**
0	/	/	/	Mild Sepsis
I	6 (3.28)	/	6 (4.76)	Mild Sepsis
Ia	3 (1.64)	/	3 (2.38)	
Ib	3 (1.64)	/	3 (2.38)	
II	72 (39.34)	9 (15.79)	63 (50.00)	Moderate Sepsis
IIa	36 (19.67)	3 (5.26)	33 (26.19)	
IIb	36 (19.67)	6 (10.53)	30 (23.81)	
III	72 (39.34)	18 (31.58)	54 (42.86)	Severe Sepsis
IIIa	33 (18.03)	6 (10.53)	27 (21.43)	
IIIb	39 (21.31)	12 (21.05)	27 (21.43)	
IV	33 (18.03)	30 (52.63)	3 (2.38)	Septic Shock
Total	183	57 (31.15)	126 (68.85)	

*IAS: Intra-Abdominal Sepsis, **PPU: Perforated Peptic Ulcer

Table 4 - Distribution of prognostic factors of death in patients with IAS* after PPU**

Prognostic factors	Total N=183	Alive n (%) 126 (68.85)	Dead n (%) 57 (31.15)	p-value
Age classes, n (%)				0.051***
< 67 years	87 (47.54)	66 (52.38)	21 (36.84)	
≥ 67 years	96 (52.46)	60 (47.62)	36 (63.16)	
Sex, n (%)				0.322***
Male	87 (47.54)	63 (50.00)	24 (42.11)	
Female	96 (52.46)	63 (50.00)	33 (57.89)	
ASA score, n (%)				<0.001***
I, II	108 (59.02)	93 (73.81)	15 (26.32)	
III, IV	75 (40.98)	33 (26.19)	42 (73.68)	
Blood transfusion, n (%)				0.485***
No	159 (86.89)	108 (85.71)	51 (89.47)	
Yes	24 (13.11)	18 (14.29)	6 (10.53)	
Causes of sepsis, n (%)				0.383***
Duodenal ulcer	105 (57.38)	75 (59.52)	30 (52.63)	
Gastric ulcer	78 (42.62)	51 (40.48)	27 (47.37)	
Fever (°C), n (%)				0.093***
37.5–38.4	24 (13.11)	18 (14.29)	6 (10.53)	
38.5–39.0	57 (31.15)	33 (26.19)	24 (42.11)	
39.1–39.5	57 (31.15)	45 (35.71)	12 (21.05)	
>39.5; <36.4	45 (24.59)	30 (23.81)	15 (26.32)	
Neutrophil count, n (%)				0.007***
40 –74	27 (14.75)	24 (19.05)	3 (5.26)	
75 –85	45 (24.59)	36 (28.57)	9 (15.79)	
85 –90	51 (27.87)	30 (23.81)	21 (36.84)	
>90; <40	60 (32.79)	36 (28.57)	24 (42.11)	
Pre-operative organ failure, n (%)				<0.001***
No	111 (60.66)	96 (76.19)	15 (26.32)	
One	39 (21.31)	27 (21.43)	12 (21.05)	
Two or more	33 (18.03)	3 (2.38)	30 (52.63)	
Immuno-compromised status, n (%)				0.252***
No	153 (83.61)	108 (85.71)	45 (78.95)	
Yes	30 (16.39)	18 (14.29)	12 (21.05)	
TNM stage, n (%)				<0.001***
0; I; II	78 (42.62)	69 (54.76)	9 (15.79)	
III; IV	105 (57.38)	57 (45.24)	48 (84.21)	

*IAS: intra-abdominal sepsis, **PPU: Perforated peptic ulcer, *** χ^2 test

were left out of the multivariate model. Multiple adjusted analysis indicated ASA score III-IV vs I-II (OR 5.99, 95% CI 2.86 - 12.57, p<0.001) and TNM stage III-IV vs 0-I-II (OR 4.49, 95% CI 1.93 - 10.44, p<0.001) as independent predictors of death in patients with duodenal or gastric ulcer (*table 5*). The model has a good predictive power being the area under the ROC curve equal to 0.8058 (standard error 0.0342) (*fig. 1*).

In the control group retrospectively analysed death occurred in 33.3% of patients, with no significant difference from the study group. The mortality increased among stages (13.1% at stage II, 28.5% at stage III and 100% at stage IV).

Table 5 - Multiple adjusted analysis between death for PPU* and independent variables present in the final model

Prognostic factors	OR°	95% CI	p-value
ASA score, n (%)			
I, II[a]	1		
III, IV	5.99	2.86 - 12.57	<0.001
TNM stage, n (%)			
0; I; II[a]	1		
III; IV	4.49	1.93 - 10.44	<0.001

*PPU: perforated peptic ulcer, [a]reference category, °adjusted odds ratios for the other variables in the model

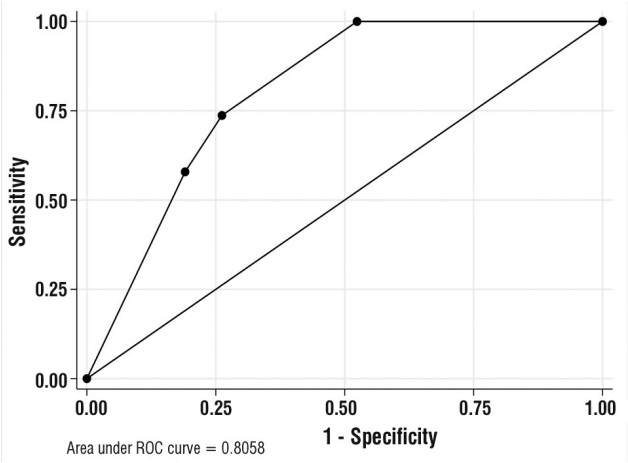

Figure 1 - Receiver operating characteristics (ROC) curve for model fit. Area under curve (AUC)=0.8058; standard error (SE)=0.0342

DISCUSSION

Mortality is a serious complication in PPU. PPU carries a mortality ranging from 1.3% to 40% (4-9,21, 22). The mortality rate is as high as 12%-47% in elderly patients undergoing PPU surgery (23-25). Significant risk factors that lead to death are presence of patients factors (age > 65 years-old, female, underweight, presence of comorbidities, delay in presentation more than 24h, non-steroidal anti-inflammatory or steroid use), disease factors (shock at presentation, elevated urea or creatinine, metabolic acidosis, anemia, hypoalbuminemia), and treatment factors (resection surgery, blood transfusion, intensive care units) (26-33). Several different scoring systems used to predict outcome in PPU can be identified through the literature: the Boey score, the ASA score, the Sepsis score (SS), the Charlson Comorbidity Index (CCI), the Mannheim Peritonitis Index (MPI), the Acute Physiology and Chronic Health Evaluation II (APACHE II), the Simplified Acute Physiology score II (SAPS II), the Physiology and Operative Severity Score for the Enumeration of Mortality and Morbidity Physical Sub-score (POSSUM-phys score), the Mortality Probability Models II (MPM II), the PULP score, the Hacettepe score (HS), the Jabalpur score (JS), the Practical Scoring System of Mortality in Patients with Perforated Peptic Ulcer (POMPP) score, and the American Association for the Surgery of Trauma (AAST) Emergency General Surgical (EGS) grading system (AAST EGS grade) (34-37). Anbalakan K. et al have validated ASA score, Boey's score, MPI and PULP score and found that all the four systems have moderate accuracy of predicting mortality with area under the receiver operator curve of 72%-77.2% (37). Other scoring systems are not widely used due a lack of validation or their complexity in clinical use. Our new scoring system (18,19) is simple to use and it seems to be a good predictor of mortality. We believe that the initial TNM stage can be easily adopted in the clinical practice to predict the surgical mortality of PPU patients. Early detection of patients at higher risk could be useful to choose other treatment strategies except surgery to decrease the risk of mortality. More consistent and careful perioperative cares should be adopted, among which respiratory support, circulatory stabilization and frequent monitorization (12,38). To early stage patients, a simple grading system may provide reduction in mortality rates.

The death rates related to complicated IAS is reported to be about 1% (39), 6.7% (40) up to 60% (41-50). The most important variable to explains the difference could be the heterogeneous population of patients and procedures (41,43,51-62). Both the anatomic source of infections and the physiologic impairment affect the outcome (63-67). In our present study we selected a homogeneous sample with the same diagnosis (complicated peptic ulcer), same operation (urgent open repair), same surgical incision (midline laparotomy).

Our results showed that TNM could help to classify patients based on their mortality risk. Moreover, some variables seem to be related to mortality: TNM stages III-IV, ASA score III-IV, neutrophil count and preoperative organ failure. Multivariate analysis, in fact, showed that TNM stage IV and ASA score IV themselves significantly influenced the mortality. Indeed, 90.9% (30/33) of the patients at stage IV died, and the high mortality rate (100%) for M2 patients was mainly reported for patients in the first period of the study (retrospective analysis), when treatment was still not so aggressive as in the last cases considered.

Our grading systems is simple and it allows a re-evaluation of the patients based on the clinical picture.

Some limitations have to be underlined. The prolonged period of data collection and the small sample size are the main ones, because these factors may influence the evaluation of the TNM. Indeed, our study population was only 183 patients, but this number was noticeable when compared with other studies in the literature (6,68-75), except cohort study of Møller 12 and the study of Hernandez (36).

A large-scale clinical trial should be evaluated.

CONCLUSION

In our preliminary study, we want to describe our results about the use of TNM score to assess IAS after PPU. This "transfer" of TNM from cancer pathology to septic pathology could prove, if other studies confirm our results, to be extremely effective to define the mortality risk in patients with IAS after PPU.

Supported and conflict of interest statement

The authors declare no dedicated source of funding and no conflicts of interest related to this publication.

Ethics approval and consent to participate

This is an observational clinical study, so ethics approval is not required. Informed consent was obtained from all individual participants included in the study.

Competing interests

The authors declare that they have no conflict of interest.

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Authors' contributions

M.S. and F.C. provided study conception and design. B.P., L.R., A.G. have acquired the data. A.M. analysed and interpreted these data. L.R. drafted the manuscript. All authors revised, read and approved the final manuscript.

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