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# The early prediction of mortality in acute cholecystitis: Temperature, Neutrophils and Multiple organ failure (TNM) score

L. ROMANO[1], A. GIULIANI[1], B. PESSIA[2], A. MATTEI[3], F. FIASCA[3], E. TONELLI[4], F. CARLEI[1], M. SCHIETROMA[1]

[1]General Surgery, Department of Surgery, University of L'Aquila, San Salvatore Hospital, L'Aquila, Italy
[2]Hepato-Biliopancreatic Surgery, Department of Surgery, San Salvatore Hospital, L'Aquila, Italy
[3]Department of Life, Health & Environmental Sciences, University of L'Aquila, L'Aquila, Italy
[4]U.O.C. di Emergenza e d'Urgenza, S. Salvatore Hospital, L'Aquila, Italy

**Abstract. – OBJECTIVE: Acute Cholecystitis (AC) accounts for a significant proportion of patients presenting to the Emergency Department with abdominal pain. We suggest grading the severity of AC with a simple system: TNM, an acronym borrowed by cancer staging where T indicated Temperature, N neutrophils and M Multiple organ failure. This retrospective-prospective observational study evaluates the predictive value of TNM score on mortality of patients with AC.**

**PATIENTS AND METHODS: TNM was developed in a training cohort of 178 patients with AC who underwent cholecystectomy from February 2005 to December 2012 (retrospectives data). To verify the prognostic value of TNM score, we prospectively recruited 172 patients who were consecutively included and treated from January 2013 to July 2020 as the validation cohort. After defining the categories T, N and M, patients were grouped in stages. The variables analyzed were age, sex, American Society of Anesthesiologists (ASA) score, blood transfusion, temperature, neutrophils count, preoperative organ failure, immune-compromised status, stage.**

**RESULTS: In the training cohort TNM staging was: none patient at stage 0; 6 patients at stage I; 71 patients at stage II; 71 patients at stage III; 30 patients at stage IV. Death occurred in 51 patients. ASA score, neutrophils count, preoperative organ failure, stage III-IV emerged as statistically significant different prognostic factors. ASA score (III-IV) and stage (III-IV) were significant independent predictors of post-operative mortality in multivariate analysis. Comparable results were observed in the validation cohort.**

**CONCLUSIONS: TNM classification is very easy to use; it helps to define the mortality risk and it is useful to objectively compare patients with AC.**

*Key Words:*
Acute cholecystitis, Intra-abdominal sepsis, Scoring systems.

## Introduction

Acute Cholecystitis (AC) is a common health problem and accounts for a significant proportion of patients presenting to the Emergency Department with abdominal pain[1]. Early diagnosis and staging of AC allow prompt treatment and reduces both mortality and morbidity. Indeed, the grading of AC is necessary for not only defining the severity of AC, but also planning early or elective cholecystectomy[2-5].

Previously, the levels of leukocytosis, C-reactive protein (CRP) and procalcitonin were assessed to predict the severity of AC, but neither was found to be useful[2-7]. The lack of standard criteria for severity assessment is reflected by the wide range of reported mortality rates in the literature: 1-3% if infection is confined to a gallbladder[8], 10-35% if infection spreads from the gallbladder and involves the peritoneal cavity[9-15].

In our paper, we proposed to classify the severity of AC with a simple grading score: TNM system. T indicates Temperature, N indicates Neutrophil count and M indicates Multiple organ failure (MOF), forming an acronym borrowed from cancer staging. This score has already been used by us for intra-abdominal sepsis by several causes and has proved to be an excellent prognostic factor for the mortality[16,17].

*Corresponding Author:* Lucia Romano, MD; e-mail: lucia.romano1989@libero.it

The aim of this retrospective-prospective observational study is to evaluate the significance of the TNM system, determined on the day of diagnosis/admission to predict mortality of patients with AC.

## Patients and Methods

For the elaboration of TNM staging, we retrospectively recruited 178 patients, who were diagnosed with AC and treated from February 2005 to December 2012 in two centers (General Surgery and Hepato-bilio-pancreatic Surgery) at our Department of Surgery as the training cohort (retrospectives data). To verify the prognostic value of TNM were recruited another 172 patients who were consecutively included and treated at our Department of Surgery from January 2013 to July 2020 as the validation cohort (prospective data). Written informed consent was obtained from all patients or their relatives (validation cohort).

The diagnosis of AC was based on the presence of the following features[8]:

**A.** Local signs of inflammation:
– Murphy's sign;
– Right upper abdominal quadrant mass/pain/tenderness.

**B.** Systemic signs of inflammation:
– Fever;
– Elevated CRP;
– Elevated white blood cells count.
– Imaging findings: characteristic of AC.

Suspected diagnosis was based on one item in A + one item in B, while definitely diagnosis was based on one item in A + one item in B +C.

Pregnant women and children below 18 years of age were excluded from the study. Patients with HIV/AIDS, with malignancies, those who received a transplant organ or were on immunosuppressive therapy were considered immune-compromised.

At the time of the admission, patients were clinically evaluated, blood test, abdominal ultrasonography and/or magnetic resonance imaging (MRI) and/or computed tomography (CT) were performed. All the electrolytic imbalances were corrected, and vital signs were restored to normal values.

Antibiotic therapy was administered, using Ciprofloxacin 200 mg i.v. every 8 hours or Amoxicillin-clavulanic 2 gr i.v. every 8 hours and Metronidazole 500 mg i.v. every 8 hours, to cover both aerobic and anaerobic bacteria. In all patients the infection was confirmed during surgical examination. All specimens were histopathologically evaluated by the same pathologist.

For each patient the data were collected by two independent researchers and stored in an electronic database. An exhaustive document was compiled with clinical and laboratory characteristic and to correctly define the severity of AC three classes were defined: Temperature (T), Neutrophil count (N) and Multiple organ failure (M). The distribution of the patients within the classes is showed in Table I, which also shows the groupings in stages (stage 0-IV), after the definition of the categories T, N and M.

TNM stage was calculated at the time of diagnosis/admission and then every day until death or discharge of patient from the surgical department. The primary endpoint of the study was to evaluate the significance of TNM stage assessed at the time of admission in predicting mortality. Thirty-day mortality was considered for the study.

### Statistical Analysis

The characteristics of the study sample were analyzed using descriptive statistics, and 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, fever, neutrophil count, pre-operative organ failure, immuno-compromised status, TNM stage) were examined between outcome groups (alive or dead). Chi square ($\chi^2$) test was used to analyze 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 recorded electronically, and 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.

**Table I.** Temperature- Neutrophil- Multiple organ failure (TNM) Staging System for AC*.

| **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 AC |
| **I** | | Mild AC |
| – Ia | T1; N0, N1; M0 | |
| – Ib | T2; N0, N1; M0 | |
| **II** | | Moderate AC |
| – IIa | T3; N0, N1, N2; M0 | |
| – IIb | T4; N0, N1, N2; M0 | |
| **III** | | Severe AC |
| – IIIa | Any T; N3; M0 | |
| – IIIb | Any T; any N; M1 | |
| **IV** | Any T; any N; M2 | Severe AC with shock |

*AC: acute cholecystitis. **Oral temperature. ***Temperature should be recorded at least 4 times in 24h.

## Results

Of the enrolled patients, 178 were included in the training cohort; there were 97 (54.5%) females and 81 (45.5%) males with a median age of 64.8 years (range 27-88).

TNM staging assessed at diagnosis on the bases of clinical findings and laboratory values was: none patient at stage 0; 6 patients at stage I; 71 patients at stage II; 71 patients at stage III; 30 patients at stage IV (Table II). Death occurred in 51 (28.6%) patients. The mean age of non-survivors was 58.1 (range 27 to 76) years, while the mean age of survivors was 62.3 (range 36 to 88) years. No patient with stage I died; mortality progressively increased (stage II: 11.7%; stage III: 37.2%) to 50.9% at the stage IV (Table II).

Statistically significant differences using $\chi^2$ test emerged for ASA score, neutrophil count, pre-operative organ failure and TNM stage between outcome groups (Table III). As neutrophil count and pre-operative organ failure are variables that define the TNM stage, they were left out of the multivariate model. Multiple adjusted analysis indicated ASA score III-IV *vs.* I-II (OR 6.02, 95% CI 2.44-13.01, $p<0.001$) and TNM stage III-IV *vs.* 0-I-II (OR 5.02, 95% CI 1.72-9.98, $p<0.001$) as independent predictors of death in patients with AC. The model has a good predictive power being the area under the ROC curve equal to 0.8621 (standard error 0.0288).

The prognostic value of TNM was further verified in an independent validation cohort of 172 patients. The results were similar to those obtained from the training cohort (Tables IV and V).

## Discussion

Patients with AC may present with a spectrum of disease stage ranging from a mild, self-limited illness to a fulminant, potentially life-threatening illness. The severity of AC in the Tokyo guidelines[8] is classified into three grades, grade I

**Table II.** Patients with AC*: Stage TNM** on the day of diagnosis/admission and mortality in the training cohort.

| Stage TNM | N° (%) | Dead N° (%) | Alive N° (%) | Clinical profile |
|---|---|---|---|---|
| 0 | / | / | / | Mild AC |
| I | 6 (3.37) | / | 6 (4.72) | Mild AC |
| – Ia | 4 (2.24) | / | 4 (3.14) | |
| – Ib | 2 (1.1) | / | 2 (1.57) | |
| II | 71 (39.88) | 6 (11.7) | 65 (51.18) | Moderate AC |
| – IIa | 36 (20.22) | 2 (3.92) | 34 (26.77) | |
| – IIb | 35 (19.66) | 4 (7.84) | 31 (24.40) | |
| III | 71 (39.88) | 19 (37.25) | 52 (40.94) | Severe AC |
| –IIIa | 32 (17.97) | 5 (9.8) | 27 (21.25) | |
| –IIIb | 39 (21.91) | 14 (27.4) | 25 (19.68) | |
| IV | 30 (16.85) | 26 (50.98) | 4 (3.14) | Severe AC with shock |
| Total | 178 | 51 (28.65) | 127 (71.34) | |

*AC: acute cholecystitis. **TNM: Temperature-Neutrophils-Multiple organ failure.

**Table III.** Patients with AC*: distribution of prognostic factors of death in the training cohort.

| Prognostic factors | Total N = 178 | Alive n (%) 127 (71.34) | Dead n (%) 51 (28.65) | *p*-value |
|---|---|---|---|---|
| Age classes, n (%) | | | | 0.048** |
| < 65 years | 85 (47.75) | 67 (52.75) | 18 (35.29) | |
| ≥ 65 years | 93 (52.24) | 60 (47.24) | 33 (64.70) | |
| Sex, n (%) | | | | 0.364** |
| Male | 81 (45.50) | 61 (48.03) | 20 (39.21) | |
| Female | 97 (54.49) | 66 (51.96) | 31 (60.78) | |
| ASA score, n (%) | | | | < 0.001** |
| I, II | 83 (46.62) | 76 (59.84) | 9 (17.64) | |
| III, IV | 95 (53.37) | 51 (40.15) | 44 (86.27) | |
| Blood transfusion, n (%) | | | | 0.378** |
| No | 155 (87.07) | 111 (87.40) | 44 (86.27) | |
| Yes | 23 (12.92) | 16 (12.59) | 7 (13.72) | |
| Fever (°C), n (%) | | | | 0.084** |
| 37.5-38.4 | 23 (12.92) | 19 (14.96) | 4 (7.84) | |
| 38.5-39.0 | 56 (31.46) | 30 (23.62) | 26 (50.98) | |
| 39.1-39.5 | 55 (30.89) | 47 (37.00) | 8 (15.68) | |
| > 39.5; < 36.4 | 44 (24.71) | 31 (24.40) | 13 (25.49) | |
| Neutrophil count, n (%) | | | | 0.007** |
| 40-74 | 24 (13.48) | 23 (18.11) | 1 (1.96) | |
| 75-85 | 43 (24.15) | 33 (25.98) | 10 (19.60) | |
| 85-90 | 48 (26.96) | 33 (25.98) | 15 (29.41) | |
| > 90; < 40 | 63 (35.39) | 38 (29.92) | 25 (49.01) | |
| Pre-operative organ failure, n (%) | | | | < 0.001** |
| No | 109 (61.23) | 98 (77.16) | 11 (21.56) | |
| One | 39 (21.9) | 25 (19.68) | 14 (27.45) | |
| Two or more | 30 (16.85) | 4 (3.14) | 26 (50.98) | |
| Immuno-compromised status, n (%) | | | | 0.368** |
| No | 149 (83.70) | 111 (87.40) | 38 (74.50) | |
| Yes | 29 (16.29) | 16 (12.50) | 9 (17.64) | |
| TNM stage, n (%) | | | | < 0.001** |
| 0; I; II | 77 (43.25) | 71 (55.90) | 6 (11.76) | |
| III; IV | 101 (56.74) | 56 (44.00) | 45 (88.23) | |

*AC: acute cholecystitis. **$\chi^2$ test.

**Table IV.** Patients with AC*: Stage TNM** on the day of diagnosis/admission and mortality in the validation cohort.

| Stage TNM | N° (%) | Dead N° (%) | Alive N° (%) | Clinical profile |
|---|---|---|---|---|
| 0 | / | / | / | Mild AC |
| I | 5 (2.90) | / | 5 (4.03) | Mild AC |
| – Ia | 3 (2.32) | / | 3 (2.41) | |
| – Ib | 2 (1.16) | / | 2 (1.61) | |
| II | 69 (40.11) | 5 (10.41) | 64 (51.61) | Moderate AC |
| – IIa | 34 (19.76) | 2 (4.16) | 32 (25.80) | |
| – IIb | 35 (20.34) | 3 (6.25) | 32 (25.80) | |
| III | 70 (40.69) | 19 (39.58) | 51 (41.12) | Severe AC |
| –IIIa | 32 (18.6) | 4 (8.33) | 28 (22.58) | |
| –IIIb | 38 (22.09) | 15 (31.25) | 23 (18.5) | |
| IV | 28 (16.27) | 24 (50.00) | 4 (3.22) | Severe AC with shock |
| Total | 172 | 48 (27.90) | 124 (72.09) | |

*AC: acute cholecystitis. **TNM: Temperature-Neutrophils-Multiple organ failure.

**Table V.** Patients with AC*: distribution of prognostic factors of death in the training cohort.

| Prognostic factors | Total N = 172 | Alive n (%) 124 (72.09) | Dead n (%) 48 (27.90) | *p*-value |
|---|---|---|---|---|
| Age classes, n (%) | | | | 0.036** |
| < 65 years | 81 (47.09) | 65 (52.41) | 16 (33.33) | |
| ≥ 65 years | 91 (52.90) | 59 (47.58) | 32 (66.66) | |
| Sex, n (%) | | | | 0.428** |
| Male | 77 (44.76) | 59 (47.58) | 18 (37.50) | |
| Female | 95 (55.23) | 65 (52.41) | 30 (62.50) | |
| ASA score, n (%) | | | | <0.001** |
| I, II | 80 (46.51) | 74 (59.67) | 6 (12.5) | |
| III, IV | 92 (53.48) | 50 (40.32) | 42 (87.5) | |
| Blood transfusion, n (%) | | | | 0.362** |
| No | 151 (87.79) | 110 (88.70) | 41 (85.41) | |
| Yes | 21 (12.20) | 14 (11.29) | 7 (14.58) | |
| Fever (°C), n (%) | | | | 0.072** |
| 37.5–38.4 | 21 (12.20) | 18 (14.51) | 3 (16.25) | |
| 38.5–39.0 | 54 (31.39) | 30 (24.19) | 24 (50.00) | |
| 39.1–39.5 | 53 (30.81) | 46 (37.09) | 7 (14.58) | |
| > 39.5; < 36.4 | 44 (25.58) | 30 (24.19) | 14 (29.16) | |
| Neutrophil count, n (%) | | | | 0.007** |
| 40-74 | 23 (13.37) | 22 (17.74) | 1 (2.08) | |
| 75-85 | 41 (23.83) | 32 (25.80) | 9 (18.75) | |
| 85-90 | 46 (26.74) | 32 (25.80) | 14 (29.16) | |
| > 90; < 40 | 62 (36.04) | 38 (30.64) | 24 (50.00) | |
| Pre-operative organ failure, n (%) | | | | < 0.001** |
| No | 106 (61.12) | 97 (78.22) | 9 (18.75) | |
| One | 38 (22.09) | 23 (18.54) | 15 (31.2505) | |
| Two or more | 28 (16.27) | 4 (3.22) | 24 (50.00) | |
| Immuno-compromised status, n (%) | | | | 0.512** |
| No | 145 (84.30) | 108 (87.09) | 37 (77.08) | |
| Yes | 27 (15.69) | 16 (12.90) | 11 (22.91) | |
| TNM stage, n (%) | | | | < 0.001** |
| 0; I; II | 74 (43.02) | 69 (55.64) | 5 (10.41) | |
| III; IV | 98 (56.97) | 55 (44.35) | 43 (89.58) | |

*AC: acute cholecystitis. **$\chi^2$ test.

(mild), grade II (moderate), and grade III (severe). Grade I (mild AC) is defined as AC in a patient with no organ dysfunction and limited disease in the gallbladder, making cholecystectomy a low-risk procedure. Grade II (moderate AC) is associated with no organ dysfunction, but there is extensive disease in the gallbladder, resulting in difficulty in safety performing a cholecystectomy. Grade III (severe AC) is defined as AC with organ dysfunction. However, this staging system is not widely used due to a lack of validation.

A new scoring system (TNM score) proposed by us[16,17], besides being very easy to use, has proven to be an excellent predictor of mortality. We believe that the initial TNM stage can be easily adopted in the clinical practice to predict the surgical mortality of AC 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[18]. To early-stage patients, a simple grading system may provide reduction in mortality rates.

The death rates due to complicated intra-abdominal sepsis reported in literature present a wide range from 1%[19], 6.7%[20,21] to 60%[22-41]. The most important factor, in our opinion, that explains this difference may be that in all studies[21,23,36-47], including our previous study[16], have entered a heterogeneous population of patients and procedures that are associated with various types of postoperative anesthetic cares. Indeed, the multifaceted nature of abdominal surgical infections makes it difficult to exactly define the disease and to assess its severity and therapeutic progress. Both the anatomic source of infections and, to a greater degree, the physiologic impairment it inflicts, affect the outcome[48-51]. For this reason, we conducted this study in which the population is relatively homogeneous including a single diagnosis (AC), one type of operation (cholecystectomy).

According to our results, it seems that TNM allows to classify patients based on their mortality risk. Moreover, there are some factors that could be directly related to mortality after AC, in particular TNM stages III-IV, ASA score III-IV, neutrophil count and preoperative organ failure. Otherwise, multivariate analysis showed that TNM stage IV and ASA score IV themselves significantly influenced the mortality. Indeed, 86.6% (26/30) of the patients at stage IV died, and this high mortality rate 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.

Therefore, our method shows a possible, simple way to classify patients with specific source of infection. Furthermore, the TNM stage is dynamic, allowing critical re-evaluation during the evolution of the clinical features.

According to the definition of sepsis and septic shock[52], we could associate septic shock to the stage IV, severe sepsis to the stage III, moderate sepsis to the stage II, and mild sepsis to the stages I and 0. At this point the grades attributed to the different characteristics of AC are widely subjective, although their order, for non-specific features, is likely exact. In this regard, we report in full what we have already written in our previous study[16]: "*Many remarks can be made on the individual scores. The range of temperature graded higher than T0 is beyond the normal value of 36.9 ± 0.47°C[53], and the score of temperature has been influenced by the findings of Altemeier et al[54] and of Elebute and Stoner[39]. The range of neutrophil count reflects the works of van Ruler et al[55-58]. An attempt has been made to score multiple organ failure, despite the difficulty of getting a precise definition universally accepted. The rating of multiple organ failure was supported by data of Goris et al[40] who in 1985 published the multiple organ failure score, grading the pulmonary, cardiovascular, hepatic, renal, nervous, haematological and gastrointestinal dysfunction on three-point scale".*

There are some limitations in this study that must be addressed. 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. Moreover, it should also be considered that a long lead time between the onset of disease and the assessment of score may contribute to the performance of the TNM.

Therefore, in order to better evaluate the TNM classification, large-scale multicenter clinical studies should follow. Our score needs further validation before being used in clinical practice.

## Conclusions

With this study, we want to share our experience and preliminary results about the application of TNM system to grade AC and to predict out-

comes. This score could also be useful to objectify the grade of AC and so to compare patients among different centers with the advantage to be very easy to use. Therefore, 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 AC.

### Conflict of Interest

The Authors declare that they have no conflict of interests.

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