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Appendix

Which prognostic score for abdominal sepsis? Analysis of final results of PIPAS (Physiological Indicators for Prognosis in Abdominal Sepsis) study in a single center

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PIPAS protocol

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Physiological Indicators for Prognosis in Abdominal Sepsis (PIPAS) Study

Background

Sepsis is a complex, multifactorial syndrome which can evolve into conditions of varying severity.

Abdominal sepsis represents the host's systemic inflammatory response to bacterial or yeast peritonitis.

In certain patient peritonitis can quickly lead to an excessive inflammatory response, and early and aggressive mechanical peritoneal control is determinant for stopping the septic process. In those patients inability to control or interrupt the local inflammatory response is associated with poor outcomes.[1] If left untreated, it may lead to the functional impairment of one or more vital organs or systems.[2]

Timing and adequacy of source control are the most important issues in the management of patients with peritonitis because inadequate and late operation may have a negative effect on outcome. In the CIAOW (Complicated intra-abdominal infections worldwide observational) study including 1898 consecutive patients older than 18 years undergoing surgery or interventional drainage to address IAI, a delayed initial intervention was found to be an independent variable predictive of mortality. In this study the overall mortality rate was 10.5% (199/1898).[3]

Early detection and timely therapeutic intervention can improve the prognosis of patients with sepsis. However, early diagnosis of sepsis can be difficult; because determining which patients presenting with signs of infection during an initial evaluation, do currently have, or will later develop a more serious illness is not an easy.

In order to validate a new practical sepsis severity score for patients with complicated intra-abdominal infections (cIAIs) including the clinical conditions at the admission (severe

sepsis/septic shock), the origin of the cIAIs, the delay in source control, the setting of acquisition and any risk factors such as age and immunosuppression a prospective study was conducted around the world from October 2014 to February 2015. The WISS study (WSES cIAIs Score Study) is a multicenter observational study underwent in 132 medical institutions worldwide during a four-month study period.[4] The data from WISS study showed that mortality was significantly affected by the old sepsis definition. Mortality by sepsis status was: no sepsis 1.2%, sepsis only 4.4%, severe sepsis 27.8% and septic shock 67.8%. Early detection and timely therapeutic intervention improved the prognosis and overall clinical outcome of patients.

In 2016 a task force convened by national societies including the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM) proposed a new definition of sepsis, termed Sepsis-3.[5]

The new definitions eliminate the terms systemic inflammatory response syndrome (SIRS), since the cause of SIRS is not always infection, and *severe sepsis*.

The new proposal defines sepsis as life-threatening organ dysfunction caused by a dysregulated host response to infection. Septic shock should be defined as a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone.

Clinically organ dysfunction can be represented by an increase in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score of 2 points or more, which is associated with an in-hospital mortality greater than 10%. It was demonstrated to be a good indicator of prognosis in critically ill patients during the first few days of ICU admission, but not as a test for sepsis. Moreover, the SOFA score is not universally accessible outside the ICUs, especially for PaO_2, which would require an arterial blood gas measurement.

Recognizing these practical limitations, the 2016 SCCM/ESICM task force described a

simplified method termed *quick SOFA* to facilitate easier identification of patients potentially at risk of dying from sepsis.

Patients are considered qSOFA-positive when they meet two of the following three criteria:

- Glasgow Coma Score <15 (which means any alteration in mentation);
- Respiratory rate ≥22 breaths/min; or
- Systolic blood pressure ≤100 mm Hg

Criticism of these new methods does exist and data has emerged illustrating the limitations of the new definitions, particularly in early detection of sepsis. Williams *et al.*[6] recently carried out a prospective database study in a tertiary Australian medical center that aimed to determine the prognostic impact of SIRS and compare the diagnostic accuracy of SIRS and qSOFA. In this study of 8871 emergency room patients, of whom 4176 (47.1%) had SIRS, SIRS was associated with an increased risk of organ dysfunction (RR 3.5) and mortality in patients without organ dysfunction (OR 3.2). SIRS and qSOFA showed similar discrimination for organ dysfunction (AUROC 0.72 *vs.* 0.73). qSOFA was specific but poorly sensitive for organ dysfunction (96.1%, 29.7% respectively).

The qSOFA is a tool for risk-stratification and it seems necessary to look for options to improve its low sensitivity.

The difference between a screening tool and a risk-stratification tool. A screening tool aims to identify patients with a particular disease from a larger pool of patients. Once these patients are identified, a risk-stratification tool can be applied to determine their likelihood of meeting a particular outcome.

We probably still need a good screening tool to identify patients at risk of developing organ dysfunction. However, this is not addressed in Sepsis-3.

An early warning score (EWS) is a guide used by medical services to quickly determine the degree of illness of a patient. It is based on the six cardinal vital signs [respiratory rate,

oxygen saturation, temperature, blood pressure, pulse/heart rate, level of consciousness (AVPU response)].

A range of Early Warning Scores have been developed in response to the needs of specific patient types.[7] There is a lack of consensus on what constitutes the 'ideal' early warning score system. Comparing different systems in clinical use shows variation in which parameters are scored and how those scores are assigned to differing levels of deterioration. There is however some evidence that certain parameters are better at predicting which patients will die than others

To compare qSOFA with other commonly used early warning scores outside the intensive care unit (ICU) a retrospective study was published in 2016.[8]

Of the 30,677 included patients, 1649 (5.4%) died and 7385 (24%) experienced the composite outcome (death or ICU transfer). Discrimination for in-hospital mortality was highest for NEWS, followed by MEWS, and SIRS. Using the highest non-ICU score of patients, ≥2 SIRS had a sensitivity of 91% and specificity of 13% for the composite outcome compared with 54% and 67% for qSOFA ≥2, 59% and 70% for MEWS ≥5, and 67% and 66% for NEWS ≥8, respectively. These results suggest that the qSOFA score should not replace general early warning scores when risk-stratifying patients with suspected infection.

Physiological deterioration often precedes clinical deterioration as patients develop critical illness. In this study, we aim to evaluate vital signs in a global cohort of patients with acute peritonitis, determining which parameters are statistically significant to predict in-hospital mortality and ICU admission.

Aims

Primary aim

The primary aim of the present study is to evaluate which bed-side parameters are statistically

significant to predict in-hospital mortality, ICU admission and the development of an ongoing (tertiary) peritonitis in patients with acute peritonitis.

Secondary aim

The most significant variables, will be adjusted to clinical criteria, and will be used to create a new bed-side early warning score for patients with acute peritonitis that will be able to associate with abdominal signs in our clinical practice.

Study population

The study will be a worldwide multicenter observational study. The study will include patients admitted in the surgical department with acute peritonitis during a four-month study period (February 1, 2018 - May 31, 2018).

Study design

The study will meet and will be conform to the standards outlined in the Declaration of Helsinki and Good Epidemiological Practices.

The study will not attempt to change or modify the clinical practice of the participating physicians: neither informed consent or formal approval by local Ethics Committee will be required because of the purely observational nature of the study.

The study will be monitored by the coordination center, which will investigate and verify missing or unclear data submitted to a central database.

The study protocol has been approved by the board of the WSES and the study will be conducted under its supervision. The board of the WSES grants the proper ethical conduct of the study.

The data collection will be anonymous, as well as the name of the patients or hospital will be

not collected in the website. Every hospital will continue following their ethical standards and local rules. The list of the submitted cases will not be recognized by investigators and linked to the submitting hospital. Individual researchers will take personal responsibility of data collection of this study.

Differences in local surgical practice of each center will be respected, no changes will be impinged on local management strategies.

The center coordinator of each participating medical institution will collect clinical data in an online case report database. Every center coordinator will be included in the Authors list.

Data will be analyzed in absolute frequency and percentage, in the case of qualitative variables. Quantitative variables will be analyzed as medians and interquartile range (IQR). Univariate analyses will be performed to study the association between risk factors and in-hospital mortality using a chi-square test, or a Fisher's exact test, if the expected value of a cell will be <5. All tests will be two-sided, and p values of 0.05 will be considered statistically significant. To investigate factors associated with death or ICU admission, we will construct a logistic regression model, including variables with P<0.05 in the univariate analysis. All statistical analyses will be performed using Stata 11 software package (StataCorp, College Station, TX).

Inclusion criteria

All patients admitted in the surgical department with acute peritonitis.

Data collection

In each center, the coordinator will collect and fill the data in an online case report system. These data included the following:

1) gender, age.

2) Presence of comorbidities:

a. primary or secondary immunodeficiency (chronic treatment with glucocorticoids, with immunosuppressive agents or chemotherapy, and patients with lymphatic diseases or with virus-related immunosuppression (HIV);

b. solid or haematopoietic and lymphoid malignancy;

c. severe cardiovascular disease (medical history of ischemic heart disease, history of heart failure, severe valvular disease[9]);

d. diabetes Type 1 or Type 2;

e. severe chronic obstructive pulmonary disease (COPD).[10]

3) Physiologic indicators at admission:

a. respiratory rate (breaths/min);

b. blood oxygen saturation level (SpO_2) (%) in air;

c. core temperature (°C);

d. systolic blood pressure (mmHg);

e. hearth rate (bpm);

f. alert/verbal/painful/unresponsive (AVPU) responsiveness scale;[11]

g. Numerical Rating Scale (NRS).[12]

4) Clinical findings upon admission, as fever (defined as core temperature >38.0°C) or hypothermia (core temperature <36.0°C), leucocytosis (white blood count [WBC] >12,000 cells/ml) or leukopenia (WBC <4000 cells/mL); presence of localized pain, diffuse pain, abdominal rigidity.

5) Parameters of Quick Sequential Organ Failure Assessment (qSOFA) upon admission.[13]

6) Setting of acquisition. Complicated IAIs will be classified as community-acquired (CA-cIAIs) or hospital-acquired (HA-cIAIs).

7) Radiological diagnosis (ultrasound, radiological and computer tomography findings).

8) Source of infection (stomach or duodenum, cholecyst, small bowel, colon, appendix or other), and peritonitis diffusion (generalized or localized peritonitis/abscess).

9) Source control (conservative treatment, operative or non-operative interventional procedures) and its adequacy, defining the latter one as the achievement to establish the cause of cIAIs and to control the origin of peritonitis.[14]

10) Delay in the initial intervention, established if the time elapsed between the admission and the performance of source control will be greater than 24 hours.

11) Reoperation during the hospital stay.

12) Length of ICU stay.

13) Length of hospital stay (LOS).

14) In-hospital mortality.

15) Post-operative complications

All patients will be monitored until they will be discharged or transferred to another ward.

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