Université de Bourgogne
UFR des Sciences de Santé
Circonscription

ANNEE 2020

N°

A vague presentation increases 28-day mortality in septic patients

Une présentation vague augmente la mortalité à 28 jours chez les patients septiques

THESE
Présentée

à l'UFR des Sciences de Santé de Dijon
Circonscription Médecine

et soutenue publiquement le 22/10/2020

pour obtenir le grade de Docteur en Médecine

par Francesco CAMPANELLI

Né(e) le 31/12/1990

A Taranto, Italie

Université de Bourgogne
UFR des Sciences de Santé
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Madame le Docteur Aurélie AVONDO
Madame le Docteur Agnès SOUDRY-FAURE

SERMENT D'HIPPOCRATE

Au moment d'être admis(e) à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions.

J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité.

Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences.

Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera.

Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admis(e) dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçu(e) à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité.

Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonoré(e) et méprisé(e) si j'y manque.

GIURAMENTO D'IPPOCRATE

"Consapevole dell'importanza e della solennità dell'atto che compio e dell'impegno che assumo, giuro:

di promuovere la salvaguardia della salute, del benessere e dei diritti degli individui e delle popolazioni come mio primo impegno professionale;

di praticare la medicina intesa come insieme di scienze applicate che si fondano sui risultati della ricerca basata sul metodo sperimentale e sull'osservazione sistematica e pianificata;

di esercitare la medicina in autonomia di giudizio senza accettare nessuna interferenza o indebito condizionamento;

di perseguire con la persona assistita una relazione di cura fondata sulla fiducia e sul rispetto dei valori e dei diritti di ciascuno e su un'informazione preliminare alla raccolta del consenso comprensibile e completa;

di informare la mia condotta ai principi di solidarietà e giustizia al fine di garantire il rispetto dei diritti civili circa l'autonomia della persona;

di curare ogni paziente con scrupolo e impegno, senza discriminazione alcuna, promuovendo l'eliminazione di ogni forma di diseguaglianza nella tutela della salute;

di adeguare la conoscenza scientifica, le applicazioni tecnologiche e le mie abilità tecniche alle specifiche caratteristiche del singolo individuo nel rispetto delle sue preferenze e delle sue sensibilità;

di non far mai prevalere l'interesse della scienza sulla salvaguardia della salute, del benessere e dei diritti dei soggetti coinvolti nella ricerca biomedica;

di garantire indipendenza nella progettazione, conduzione, analisi e interpretazione dei risultati degli studi clinici e di impegnarmi a rendere sempre pubblici i risultati completi delle ricerche, qualunque ne sia l'esito.

di non compiere mai atti finalizzati a provocare la morte;

di non intraprendere né insistere in procedure diagnostiche e interventi terapeutici clinicamente inappropriati ed eticamente non proporzionati, senza mai abbandonare la cura del malato;

di affidare la mia reputazione professionale alle mie competenze e al rispetto delle regole deontologiche e di evitare, anche al di fuori dell'esercizio professionale, ogni atto e comportamento che possano ledere il decoro e la dignità della professione;

di ispirare la soluzione di ogni divergenza di opinioni al reciproco rispetto delle persone coinvolte;

di prestare soccorso nei casi d'urgenza e di mettermi a disposizione dell'Autorità competente, in caso di pubblica calamità;

di rispettare il segreto professionale e di tutelare la riservatezza su tutto ciò che mi è confidato, che osservo o che ho osservato, inteso o intuito nella mia professione o in ragione del mio stato o ufficio;

di prestare, in scienza e coscienza, la mia opera, con diligenza, perizia e prudenza e secondo equità, osservando le norme deontologiche che regolano l'esercizio della professione."

REMERCIEMENTS

Voici le petit coin « intime » de ce travail.
On ne parlera pas de médecine, bien entendu, mais plutôt de tout ce qu'il y a eu autour pendant ces dernières années.

Je commencerai par les remerciements officiaux.
Je tiens donc à remercier les membres de mon jury, qui ce jour sont là pour écouter et évaluer les résultats de mon travail.

Monsieur le Professeur Patrick Ray, coordinateur local du DES de Médecine d'Urgence et Président de jury aujourd'hui. Merci de m'avoir aidé à réaliser mes projets et merci d'avoir partagé avec moi la bataille de la Médecine d'Urgence en Bourgogne. Mon voyage dans la branche de la « médecine critique » part de vos enseignements, et, un jour, ça me ferait plaisir de partager avec vous tout ce que j'aurai appris en travaillant côté à côté.

Monsieur le Professeur Pierre-Emmanuel Charles, coordinateur du DES de Médecine Intensive et Réanimation ainsi que directeur de ma thèse. Merci de m'avoir suivi et encadré lors de la réalisation de cette œuvre. Merci du soutien. Merci des opportunités. J'espère que vous aurez d'autres enseignements à me donner, dans un futur pas loin.

Monsieur le Professeur Pascal Chavanet, PUPH de Maladies Infectieuses et Tropicales au CHU de Dijon. Merci d'être là ce jour si important. Votre présence honore et complète la triade des thématiques de cette thèse, ainsi que mes intérêts les plus grands dans l'univers de la Médecine.

Madame le Docteur Aurélie Avondo, bientôt collègue, mais, surtout, amie. Merci de ton aide dans les moments difficiles, et merci de ta présence lorsque je me sentais perdu dans mon parcours long et compliqué.
Je suis honoré et ravi de t'avoir dans mon jury.

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Eccoci qua, già la seconda volta.
Sempre in preda al panico, all'ultimo momento. Agitato al pensiero d'esser davanti a loro, vestito elegante e sicuro delle mie parole. La voglia di mostrare dove questo viaggio mi ha portato, cosa mi ha reso, chi sono adesso.
Quello che forse non sanno, è che son loro il mio viaggio.
E, si sa, non è la destinazione che conta, ma il percorso.
C'è chi è stato una piccola tappa, piccola, ma unica nel suo genere ; c'è chi è stato, ed è, e sarà tutti i chilometri che ho alle spalle e tutta quella strada così irta e tortuosa che ho davanti.
A differenza dell'ultima volta, oggi loro son tanti, e son loro che trasformano la salita in una semplice passeggiata.

Ça y est, déjà la deuxième fois.
Toujours en train de paniquer, au dernier moment. Agité à l'idée d'être devant eux, bien habillé et sûr de mes mots. Avec l'envie de montrer où ce voyage m'a emmené, ce qu'il m'a rendu, qui je suis maintenant.
Ce qu'ils probablement ne savent pas, c'est que mon voyage c'est eux.
Et, tout le monde le sait, ce n'est pas la destination qui compte, mais le parcours.
Il y a qui a été une petite étape, petite, mais unique dans son genre ; il y a qui a été, est et sera tous les kilomètres que j'ai derrière moi ainsi que cette route si raide et tortueuse que je vois devant.
Contrairement à la dernière fois, ce jour ils sont nombreux, et c'est eux qui transforment la montée en une simple balade.

Ci sono i miei genitori, i miei pilastri, le mie fondamenta, il mio appiglio, la forza, il sostegno, l'amore, e, spesso, la salvezza. Primum movens et dulcis in fundo.
Uno dei miei più grandi desideri è di renderli orgogliosi.
Ci sono tutti i miei famigliari, da sempre.
La nonna, solo qualche secondo, qualche parola attraverso la cornetta per scansare fatica e tristezza. Per star bene.
Gli zii ed i cugini, che da lontano fanno il tifo. Che chiedono, si informano. Che son lì, capiscono e spronano, proprio quando serve.
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C'è il Baretto : Vale, Nico, Elio, Anton, Giulio, Zukki e (S)bozzo. "Les copains d'abord", dei fratelli. Confidenti e consiglieri. Una gran risata che io sia triste o felice. Avrebbero fatto di tutto per esser qui oggi, ed io so che ci sono. Come sempre.
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Et puis il y a ma nouvelle vie, ici en France.
Le changement, et au même temps le retour aux vieilles habitudes et attitudes, mais avec un gros bagage avec moi. La découverte d'un nouveau Pays, d'une nouvelle culture.
De nouvelles personnes.
Merci à eux. Merci de m'accompagner, me de m'apprendre, merci d'être mon voyage.
Merci de me donner envie d'un nouveau « chez moi ».
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« Quisque faber fortunae suae est ».

C

TABLE DES MATIERES ET ICONOGRAPHIES

ABBREVIATIONS

aOR : Adjusted Odds Ratio
ARDS : Acute Respiratory Distress Syndrome
BT : Body Temperature
CI : Confidence Interval
CKD : Chronic Kidney Disease
COPD : Chronic Obstructive Pulmonary Disease
DAP : Diastolic Arterial Pressure
DVT : Deep Venous Thrombosis
ED : Emergency Department
GCS : Glasgow Coma Scale
GI : Gastrointestinal
ICD : International Classification of Diseases
ICU : Intensive Care Unit
LOS : Length Of Stay
MAP : Mean Arterial Pressure
MICU : Medical Intensive Care Unit
OR : Odds Ratio
PAOD : Peripheral Arterial Occlusive Disease
qSOFA : quick Sequential Organ Failure Assessment
SAP : Systolic Arterial Pressure
SOFA : Sequential Organ Failure Assessment
SSC : Surviving Sepsis Campaign
SST : Skin and Soft Tissues

ABSTRACT

Background: Sepsis is defined as a dysregulated host response to an infection that can rapidly lead to death. Early identification of sepsis is therefore mandatory in order to prevent any delayed management, but sometimes clinical presentation is misleading. Since little is known about the determinants as well as the impact of the so-called “vague” presentation, this issue was addressed herein.

Methods: All the patients who presented at the Emergency Department (ED) and were thereafter admitted to the Intensive Care Unit (ICU) with a final diagnosis of sepsis over a three-year period, were included. They were then classified as having exhibited “vague” or explicit presentation at the ED on the basis of published criteria. Firstly patients’ baseline characteristics, infection main features and sepsis management were compared. Thereafter, we evaluated the impact of a vague presentation on 28-day mortality.

Results: Among the 348 included patients, 103 (29.6%) had an implicit sepsis presentation at the ED. Underlying diseases were more likely in those latter patients, but they were less severe in terms of organ failure at the ED. Moreover, bacteremia was less frequent in this group. In contrast, 28-day mortality was higher in the vague presentation group (40.8% vs. 26.9%, $p = 0.011$), along with longer time-to-diagnosis, time-to-antibiotics and time to ICU admission. however, such an implicit presentation of sepsis was found to be the only independent predictor of death at day-28 (adjusted odds ratio 2.14, 95% CI, 1.24-3.68, $p = 0.006$), together with age, SOFA score at diagnosis and body temperature at the ED.

Conclusion: Almost one third of septic patient requiring ICU had an implicit presentation at the ED. Despite an apparent lower level of severity when initially assessed, patients who demonstrated a vague sepsis presentation was independently associated with an increased risk of death at day-28 that could not be fully explained by delayed diagnosis and management, in accordance with previously published data.

BACKGROUND

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection, leading to a risk of death ranging from 15% to 40%, if septic shock (i.e., circulatory and cellular/metabolic failure) occurred (1, 2). Given the disease burden worldwide (3-5) and its high mortality rate, efforts have been done in order to improve sepsis outcome.

Accordingly, early diagnosis and therapy including appropriate antibiotics and fluid administration within the first hour are the cornerstone of sepsis management (6).

However, sepsis early recognition maybe challenging since infection signs are not always obvious.

Actually, suspecting sepsis relies on the diagnosis of infection together with the quick Sepsis-related Organ Failure Assessment (qSOFA) score calculation.

Although qSOFA implementation is part of the Surviving Sepsis Campaign (SSC) guidelines, its screening value has been repeatedly questioned, given its low negative predictive value (7, 8).

As a result, presenting symptoms, if not clearly and immediately suggestive of infection (i.e. the so-called vague symptoms), could delay sepsis recognition, especially upon admission in the emergency department (ED), and in turn appropriate therapy might not be started on time. However, little is known by now about vague symptoms occurrence in patients finally diagnosed with sepsis. In addition, whenever clinical presentation of infection is predictive of patient outcome and should thereby influence initial management of sepsis remain to be more extensively evaluated.

In a retrospective cohort study, Filbin et al. found that about one third of septic patients presented to the ED with vague symptoms as defined by the authors. Moreover, in-hospital mortality was significantly higher in such patients if compared with those in whom infection was obvious (9). Accordingly, other authors have reported that normothermia was not infrequent in septic patients and was associated with a poorer outcome as compared with fever (10-12).

However, published data are scarce and the reasons why clinical initial presentation influences the outcome deserve further investigations. Actually, the lack of prompt and adequate management of sepsis in the patients with vague symptoms did not necessarily account for the whole difference of survival reported in those studies.

We addressed therefore this issue in a cohort of patients with a final diagnosis of sepsis, evaluated in the ED before Intensive Care Unit (ICU) admission.

METHODS

Study Design

A retrospective monocentric cohort study was conducted from January 1, 2016, to December 31, 2019.

All adult patients (≥ 18 years old) who presented at the ED of the Centre Hospitalier Universitaire de Dijon and were then hospitalized in the Medical Intensive Care Unit (MICU), directly or after an initial hospitalization in another hospital unit, were considered for inclusion.

Inclusion and Exclusion Criteria

We included all the patients who met the following criteria: (i) at least one diagnosis code for any kind of infection according to the International Classification of Diseases, 10th edition (ICD-10); (ii) a confirmed source of infection or a highly suspected infection according to the medical chart content; (iii) the presence of sepsis or septic shock criteria according to the Sepsis-3 experts panel at any time between ED admission and transfer to the ICU .

Patients who had been treated for infection before ED arrival were excluded as well as those who were primarily hospitalized for a non-septic reason and who developed an infection during hospitalization.

Definition of Explicit and Implicit Presentation

Presenting symptoms were collected from triage and/or physician/resident doctor's notes at the ED.

We defined patient presentation as "explicit" according to the criteria used by Filbin et al. and detailed below, since it was considered to rapidly lean the clinician to consider infection. Thus, explicit symptoms for infection were: hyperthermia or hypothermia (core temperature ≥ 38.5 °C or < 36 °C, respectively), chills, SAP ≤ 90 mmHg or MAP ≤ 65 mmHg, cough with productive sputum, dysuria, reported skin redness or concern for soft-tissue infection, referral for specific diagnosis of infection.

We defined patient presentation as "implicit" or vague, if symptoms at the ED did not include any of the explicit symptoms listed above.

Data Collection

We obtained all the data from the electronic medical record system of the hospital.

Patient baseline characteristics and past medical conditions were listed. Vital stats at the ED arrival were collected, and qSOFA value was calculated.

Day 1 SOFA score was calculated upon infection was suspected according to current sepsis definitions.

Time-to-infection suspicion, time-to-antibiotic administration and time-to-ICU hospitalization were calculated from the first medical contact.

First-line antibiotic treatment was considered appropriate if effective on the latter-identified pathogen, according to the antibiotics susceptibility testing data.

Outcomes

The primary outcome was all cause 28-day mortality.

The secondary outcomes were : (i) the rate of sepsis complications that occurred during the hospital stay, including atrial fibrillation, acute hearth failure, acute coronary syndrome, cardiac arrest, acute respiratory distress syndrome (ARDS), acute kidney injury, Glasgow Coma Scale (GCS) drop > 2 points, metabolic acidosis, acute hepatic failure; (ii) the overall ICU length of stay (LOS) and hospital LOS.

Statistical Analysis

In a first set of analysis, patients with vague presentation were compared with those without.

Categorical variables were compared with the chi-square test and the Mann-Whitney test was used to compare continuous variables. In an attempt to identify covariates likely to be independently associated with vague presentation, a multivariate analysis based on a logistic regression model was conducted. Covariates were selected if the p value was less than 0.2 by univariate analysis or if it was considered as clinically relevant.

In a second set of analysis, outcomes including day 28 mortality were assessed. Based on the findings reported by Filbin et al., we hypothesized that the day-28 mortality rate would rise from 15 to 30% in patients with vague symptoms as compared to those with explicit sepsis. We then calculated a sample size of 348 patients in order to reach a statistical power of 0.80.

Day-28 survival was then analysed through the corresponding Kaplan-Meier curves construction (i.e., vague vs. explicit), which were compared with the log-rank test. Potential explanatory variables

were then assessed through univariate analysis as described above. Likewise, independent predictors for d-28 mortality were sought through a regression logistic model construction.

A *p* value of less than or equal to 0.05 was used as the cut-off for all tests of statistical significance. The JASP software version 0.13.1 was used for all analysis.

RESULTS

Study Population

From January 1, 2016, to December 31, 2019, 770 patients who presented at the ED and were then hospitalized in the ICU had a sepsis diagnosis. 422 (55%) were excluded from our study since 335 (43.5%) were initially hospitalized for another reason than sepsis or septic shock, and 87 (11.5%) had an antibiotic treatment before arriving at the ED.

348 patients were finally included in our study. Of them, 245 (70%) had an explicit presentation for sepsis, and 103 (30%) had a vague presentation (Fig. 1).

Baseline characteristics differed between the two groups regarding underlying diseases since peripheral arterial occlusive disease (PAOD) and chronic kidney disease (CKD) were more likely in the patients with vague presentation of sepsis (23.3% vs. 13.5%, p = 0.02, and 18.5% vs. 14.7%, p = 0.05, respectively), whereas asthma and haematological malignancies were more frequent in the other group (6.9% vs. 1.0%, p = 0.02, and 15.1% vs. 6.8%, p = 0.03, respectively) (Tab. 1).

Upon ED admission, patients with an implicit presentation had higher blood pressure levels (e.g., mean arterial pressure [SD]: 93 [19] vs. 79 [21] mmHg, p <.001), lower core temperature (37.1 [0.7] °C vs. 37.6 [1.9] °C, p <.001) and lower qSOFA value (0.8 [0.8] vs. 1.3 [0.8], p <.001).

Although the difference did not reach statistical significance, mean SOFA score at the time of infection diagnosis was also found to be lower if clinical presentation was vague (4.7 [3.2] in the implicit group vs. 5.2 [3.1] in the explicit group, p = 0.09) (Tab. 4).

We sought then which baseline and sepsis characteristics could be independently associated with the vague presentation of sepsis. Thus, underlying haematological malignancies was less likely in those patients (adjusted OR = 0.26, 95% CI, 0.09-0.73, p = 0.011), as well as bacteremia occurrence (adjusted OR = 0.53; 95% CI, 0.29-0.98, p = 0.04) and asthma (adjusted OR = 0.13, 95% CI, 0.02-0.97, p = 0.046). PAOD was independently associated with a vague presentation (adjusted OR 2.01, 95% CI, 1.08-3.77, p = 0.028) (Tab. 2). In contrast, sources of infection were similar between the two groups, with a slight prevalence of biliary infections in the implicit presentation group.

Patients' Management at the ED

As expected, the diagnosis of sepsis was more frequently achieved upon the ED in the explicit presentation group (86.1% vs. 62.1%, p < .001). Similarly, time-to-diagnosis was longer in the implicit group (mean delay, 18 [31] vs. 4 [11] hours, p < .001), as well as the time-to-antibiotic administration (mean delay, 20 [32] vs. 7 [12] hours, p < .001).

Similarly, the time elapsed between ED and ICU admission was longer in the patients with vague presentation than in others (mean delay, 71 [159] vs. 24 [69] hours, p < .001).

Overall, empirical antibiotics were adequate in 177/348 patients (50.9%), since susceptibility data were not available for 78/348 patients (22.4%). The treatment was less frequently appropriate in the patients with vague presentation (44.6%), than in others (53.6%), but the difference was not significant (Tab. 5).

Patients' Outcomes

Patients in the vague/implicit presentation group had a significantly higher day 28 mortality than those with explicit sepsis (40.8% vs. 26.9%, p = 0.011) (Tab. 5).

After adjustment for potential confounders, vague presentation of sepsis remained significantly associated with day 28 mortality (Tab. 6 and Tab. 7).

Similarly, the Kaplan-Meier survival analysis showed a significative difference between the two groups (p = 0.016) (Fig. 2).

Other outcomes were also assessed. Thus, among sepsis complications, cardiac arrest and acute hepatic failure were more frequent (14.6% vs. 5.7%, p = 0.006, and 13.6% vs. 6.9%, p = 0.047, respectively), in the patients with vague presentation. In contrast, mean overall hospital LOS was similar (19 [18.8] days vs. 17.4 [16.3] days, p = 0.63), as well as the ICU LOS (6.5 [9.2] days vs. 5.8 [7.7] days, p = 0.24) (Tab. 5).

DISCUSSION

We show herein that vague presentation is common in septic patients in the ED, since it was found in about 30% of them. Moreover, the absence of explicit symptoms was associated with a poorer outcome despite an apparently lower level of clinical severity in terms of organ failure.

Interestingly, our findings suggest that some underlying diseases such as hematological malignancies, promoting large bacterial inoculum, could prevent from a vague presentation of sepsis. In addition, it is worth noting that bacteremia was unlikely in those patients. Altogether, these results suggest that vague presentation including frequent normothermia, could reflect differences regarding the inflammatory response features and magnitude. One could thus speculate that the host immune response could be mitigated when clinical presentation of sepsis was vague, as compared to the one encountered in patients with much more explicit symptoms.

Unravelling the inflammatory response patterns through key mediators measurements would be thereby of great interest in order to find out the molecular basis of these clinical findings.

Accordingly, cumulative data suggest that there is a strong link between sepsis clinical and biological features, and outcome (13, 14). Thus, Seymour et al. recently identified four distinct sepsis phenotypes with various risk of mortality as well as treatment responsiveness (15).

Similarly, genomic and transcriptomic data have emphasized to which extent survival could be tightly related to some genes expression patterns (16-19). To determine to which extent the vague presentation of sepsis could be correlated with peculiar patterns of the host immune response deserves further studies.

Accordingly, it is well known that immunoparalysis frequently complicates sepsis (20).

Given the increased risk of death in the patients with vague presentation, one could hypothesize that the lack of infection signs and symptoms reflects such a depressed immune response, thereby hampering the host ability to clear pathogens. More research is needed in order to address this issue.

However, other explanatory hypothesis should be raised. Basically, delayed sepsis recognition could account for the higher day 28 mortality rate reported in the implicit group, as compared to the patients with obvious signs of infection, since it occurred 14 hours earlier in these ones. Actually and expectedly, antibiotics administration as well as transfer toward the ICU were also achieved significantly later in this group. Given the known impact of any delay in sepsis management, especially the door-to-needle time as far as antibiotics are concerned, this could account for the poorer prognosis of the patients in whom the diagnosis of infection is hard (21-23). However, vague presentation remains associated with a poor outcome even after adjustment for these factors, suggesting that the lack of symptoms could be involved by it-self, thus confirming previously published data (9). As expected, age, SOFA score value and body temperature were also independent risk factors for death at day 28 (24-27) (Fig. 3).

Interestingly, initial empirical antibiotic treatment tended to be more frequently adequate in the explicit group (53.6% vs. 44.6%, p = 0.13), although this difference was not significative. Maybe, this could be explained by an easier infection source identification thanks to the presence of more explicit symptoms.

Patients without fever are less likely to be suspected of infection than others. As expected, hyperthermia was infrequent in the included patients with vague presentation. In addition, we found a correlation between body temperature at ED arrival and 28-day mortality. Whereas hypothermia (i.e. body temperature < 36 °C) had a rough OR for mortality of 2.08, fever (i.e. body temperature ≥ 38.5 °C) had a rough OR for mortality of 0.29. These results are consistent with a work of Tiruvoipati et al., who found that hypothermia in the first 24 hours of presentation is associated with higher in-hospital mortality (28). In accordance with those findings, Young et al. have reported that an elevated peak temperature in the first 24 hours in ICU is associated with a decreased in-hospital mortality (11). Moreover, Kushimoto et al. suggested the addition of hypothermia to qSOFA to improve its ability predictive to predict mortality (29).

This study has several limitations. Firstly, given its retrospective design, some patient's data were sometimes missing or lack of accuracy. Secondly, it was a monocentric study. Differences in terms of population characteristics, local epidemiology and provided care may thus exist. As a result, it could be hazardous to translate our findings to another population.

CONCLUSIONS

Almost one third of septic patient requiring intensive cares had an implicit presentation at the ED. Despite an apparent less severity initially, such a vague presentation of sepsis was associated with a significantly higher 28-day mortality, independently from delayed diagnosis and management. Although further studies are needed, our findings are in accordance with previously published data and provide new insights into this topic. Finding out the immunological and molecular basis of the vague presentation of sepsis deserves future investigations. This could be helpful for designing new and personalized therapeutical approaches of sepsis according to the clinical presentation.

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CONCLUSIONS

Presque un tiers des patients septiques admis en réanimation avaient une présentation vague/implicite aux Urgences. Une telle présentation clinique du sepsis, malgré une sévérité apparente moins marquée, était un facteur de risque indépendant de mortalité à 28 jours, sans que les retards au diagnostic et à l'antibiothérapie qui en découlent ne puissent l'expliquer en totalité. Bien qu'il soit nécessaire de confirmer ces résultats, ils confirment le peu de données publiées à ce sujet, et incitent à mieux analyser ce sous-groupe de patients septiques, toujours exclus des essais cliniques, notamment en termes de réponse immune à l'infection.

Le Président du jury.

Pr.

Vu et permis d'imprimer
Dijon, le 7 Octobre 2020
Le Doyen

Pr. M. MAYNADIÉ

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Tab. 1: Baseline characteristics of patients with or without vague presentation at the ED. OR = Odds Ratio, CI = Confidence Interval, CHF = Chronic Heart Failure, PAOD = Peripheral Arterial Occlusive Disease, DVT = Deep Venous Thrombosis, COPD = Chronic Obstructive Pulmonary Disease, CKD = Chronic Kidney Disease, SST = Skin and Soft Tissues, GI = Gastrointestinal

Total, n = 348	**Explicit n = 245**	**Implicit n = 103**	**OR**	**95% CI**	***P***
Demographics					
Age, median year (IQR)	70.6 (50–90)	71.1 (52–90)	1.002	0.98-1.02	0.72
Gender female (%)	98 (40)	32 (31)	0.68	0.41-1.10	0.12
Smoke (%)	75 (30.6)	34 (33)	1.12	0.68-1.83	0.66
Alcohol (%)	47 (19.2)	28 (27,2)	1.57	0.92-2.69	0.09
Underlying diseases					
Hypertension (%)	121 (49.4)	59 (57.3)	1.37	0.86-2.19	0.18
CHF (%)	47 (19.2)	19 (18.4)	0.95	0.53-1.72	0.87
Myocardial Infarction (%)	49 (20)	24 (23.3)	1.22	0.69-2.11	0.49
Atrial Fibrillation (%)	77 (31.4)	35 (34)	1.12	0.69-1.83	0.64
PAOD (%)	33 (13.5)	24 (23.3)	1.95	0.09-3.51	0.025
DVT (%)	27 (11)	10 (9.7)	1.95	1.09-3.51	0.72
Diabetes mellitus (%)	76 (31)	29 (28.2)	0.87	0.53-1.45	0.59
COPD (%)	34 (13.9)	18 (17.5)	1.31	0.70-2.45	0.39
Asthma (%)	17 (6.9)	1 (1)	0.13	0.02-1.00	0.05
CKD (%)	36 (14.7)	19 (18.5)	1.31	0.71-2.42	0.38
Stroke (%)	19 (7.8)	14 (13.6)	1.87	0.89-3.89	0.09
Neurocognitive disease (%)	18 (7.3)	10 (9.7)	1.35	0.60-3-05	0.46
Cirrhosis (%)	18 (7.3)	6 (5.8)	0.78	0.30-2.03	0.61
Immunosuppressive drugs (%)	43 (17.6)	12 (11.6)	0.62	0.31-1.23	0.17
Haematological malignancy (%)	37 (15.1)	7 (6.8)	0.41	0.18-0.95	0.03
Solid cancer (%)	56 (22.9)	25 (24.3)	1.08	0.63-1.86	0.78

Tab. 1 (continued): Baseline characteristics of patients with or without vague presentation at the ED

Total, n = 348	Explicit n = 245	Implicit n = 103	*P*	OR	95% CI
Infection description					
Infection site					
Pneumonia (%)	117 (47.8)	52 (50.5)	0.64	1.12	0.70-1.77
Urinary tract infection (%)	53 (21.6)	14 (13.6)	0.085	0.57	0.30-1.08
SST infection %)	16 (6.5)	4 (3.9)	0.34	0.58	0.19-1.77
GI source of infection (%)	14 (5.7)	6 (5.8)	0.97	1.02	0.38-2.73
Biliary source of infection %)	7 (2.9)	10 (9.7)	0.011	3.66	1.35-9.89
Bacteremia (%)	91 (37.1)	26 (25.2)	0.03	0.57	0.34-0.96

Tab. 2: Adjusted odds ratio for vague presentation. aOR = adjusted Odds Ratio, CI = Confidence Interval

Covariate	aOR	95% CI	*P*
PAOD	2.01	1.08-3.77	0.028
Asthma	0.13	0.02-0.97	0.046
Haematological malignancy	0.34	0.14-0.83	0.018
Biliary source of infection	3.99	0.29-0.84	0.009
Bacteremia	0.49	0.29-0.84	0.010

Tab. 3: Confirmed pathogen according to the clinical presentation of sepsis

Pathogen	Explicit n = 245	Implicit n = 103	*p*
S. aureus (%)	15 (6.1)	8 (7.8)	0.57
S. pneumoniae (%)	17 (6.9)	3 (2.9)	0.14
E. coli (%)	55 (22.4)	11 (10.7)	0.013
K. pneumoniae (%)	6 (2.4)	9 (8.7)	0.09
P. aeruginosa (%)	10 (4.1)	5 (4.4)	0.61

Tab. 4: Severity criteria of infection at the ED according to the clinical presentation of sepsis. ED = Emergency Department, SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure, MBP = Mean Blood Pressure, GCS = Glasgow Coma Scale, SOFA = Sequential Organ Failure Assessment

Total, n = 348	Explicit n = 245	Implicit n = 103	*p*
SBP, mean mmHg (SD)	111 (31)	132 (29)	< .001
DBP, mean mmHg (SD)	63 (18)	73 (17)	< .001
MBP, mean mmHg (SD)	79 (21)	93 (19)	< .001
Hearth Rate, mean (SD)	101 (28)	98 (27)	0.18
SpO2, mean % (SD)	93 (7)	93 (7)	0.57
Respiratory Rate, mean (SD)	27 (8)	30 (12)	0.26
GCS, median (IQR)	14 (1)	14 (0)	0.27
Body Temperature, mean °C (SD)	37.6 (1.9)	37.1 (0.7)	< .001
qSOFA, mean (SD)	1.3 (0.8)	0.8 (0.8)	< .001
SOFA at sepsis diagnosis, mean (SD)	5.2 (3.1)	4.7 (3.2)	0.09

Tab. 5: Patients' management at the ED and outcomes according to the clinical presentation of sepsis. ED = Emergency Department, ICU = Intensive Care Unit, ARDS = Acute Respiratory Distress Syndrome, GCS = Glasgow Coma Scale, LOS = Length Of Stay

Total, n = 348	**Explicit n = 245**	**Implicit n = 103**	***p***
Sepsis management			
ED wait, mean minutes (SD)	48 (68)	41 (66)	0.82
Sepsis diagnosis upon the ED (%)	211 (86.1)	64 (62.1)	< .001
Time to sepsis diagnosis, mean hours (SD)	4 (11)	18 (31)	< .001
Time to antibiotics, mean hours (SD)	7 (12)	20 (32)	< .001
Time to ICU admission, mean hours (SD)	24 (69)	71 (159)	< .001
Appropriate antibiotics (%)	131 (53.5)	46 (44.6)	0.13
Outcomes			
28-day Mortality (%)	66 (26.9)	42 (40.8)	0.011
In-hospital Mortality (%)	69 (28.2)	47 (45.6)	0.002
Infection site identification (%)	234 (95.5)	97 (94.2)	0.59
Atrial Fibrillation (%)	48 (19.6)	30 (29.1)	0.052
Pulmonary Embolism (%)	5 (2)	4 (3.8)	0.32
Acute Hearth Failure (%)	49 (20)	23 (22.3)	0.62
Acute Coronary Syndrome (%)	11 (4.5)	5 (4.9)	0.88
Cardiac arrest (%)	14 (5.7)	15 (14.6)	0.006
ARDS (%)	47 (19.2)	20 (19.4)	0.96
Acute Kidney Injury (%)	182 (74.3)	72 (69.9)	0.40
CGS drop > 2 (%)	68 (27.8)	38 (36.9)	0.09
Metabolic Acidosis (%)	123 (50.2)	53 (51.5)	0.83
Acute Hepatic Failure (%)	17 (6.9)	14 (13.6)	0.047
ICU LOS, mean days (SD)	5.8 (7.7)	6.5 (9.2)	0.24
Overall LOS, mean days (SD)	17.4 (16.3)	18.8 (19)	0.63

Tab. 6: Crude odds ratio for all cause death at day 28. OR = Odds Ratio, CI = Confidence Interval, CHF = Chronic Heart Failure, PAOD = Peripheral Arterial Occlusive Disease, DVT = Deep Venous Thrombosis, COPD = Chronic Obstructive Pulmonary Disease, CKD = Chronic Kidney Disease, ED = Emergency Department, SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure, MBP = Mean Blood Pressure, GCS = Glasgow Coma Scale, SOFA = Sequential Organ Failure Assessment, SST = Skin and Soft Tissues, GI = Gastrointestinal

Total, n = 348	**28-day survivors n = 240**	**28-day non-survivors n = 108**	**OR**	**95% CI**	***p***
Age, median year (IQR)	70 (50-90)	79 (61-97)	1.04	1.02-1.06	<.001
Gender female (%)	85 (35.4)	45 (41.7)	1.30	0.82-2.07	0.26
Smoke (%)	85 (35.4)	24 (22.2)	0.52	0.31-0.88	0.014
Alcohol (%)	56 (23.3)	19 (17.6)	0.70	0.39-1.25	0.23
Arterial Hypertension (%)	114 (47.5)	66 (61.1)	1.74	1.09-2.76	0.019
Chronic Heart Failure (%)	44 (18.3)	22 (20.3)	1.14	0.64-2.02	0.65
Myocardial Infarction (%)	51 (21.3)	22 (20.3)	0.95	0.54-1.66	0.85
Atrial Fibrillation (%)	70 (29.2)	42 (38.9)	1.54	0.96-2.49	0.072
PAOD (%)	36 (15)	21 (19.4)	1.37	0.75-2.48	0.30
DVT (%)	29 (12.1)	8 (7.4)	0.58	0.26-0-32	0.19
Diabetes Mellitus (%)	70 (29.2)	35 (32.4)	1.16	0.71-1.90	0.54
COPD (%)	33 (13.8)	19 (17.6)	1.34	0.72-2.48	0.35
Asthma (%)	15 (6.3)	3 (2.8)	0.43	0.12-1.51	0.18
CKD (%)	34 (14.2)	21 (19.4)	1.46	0.80-2.66	0.21
Stroke (%)	21 (8.8)	12 (11.1)	1.30	0.61-2.76	0.49
Cirrhosis (%)	15 (6.3)	9 (8.3)	1.36	0.58-3.22	0.48
Immunosuppressive Drugs (%)	39 (16.3)	16 (14.8)	0.89	0.48-1.67	0.73
Haematological malignancies (%)	32 (13.3)	12 (11.1)	0.81	0.40-1.65	0.56
Solid cancer (%)	58 (24.2)	23 (21.3)	0.85	0.49-1.47	0.56

Tab. 6 (continued): Crude odds ratio for all cause death at day 28

Total, n = 348	28-day survivors n = 240	28-day non-survivors n = 108	OR	95% CI	*p*
ED diagnosis (%)	196 (81.7)	79 (73.1)	0.61	0.36-1.05	0.07
BT ≥ 38.5°C (%)	87 (36.3)	19 (17.6)	0.37	0.21-0.66	<.001
BT < 36°C (%)	25 (10.4)	21 (19.4)	2.08	1.10-3.90	0.02
SBP ≤ 90 mmHg (%)	56 (23.3)	18 (16.7)	0.66	0.36-1.18	0.16
MBP ≤ 65 mmHg (%)	59 (24.6)	17 (15.7)	0.57	0.31-1.04	0.065
Productive cough (%)	34 (14.2)	8 (7.4)	0.48	0.22-1.09	0.07
Dysuria (%)	6 (2.5)	1 (0.9)	0.36	0.04-3.06	0.33
Skin Redness (%)	8 (3.3)	3 (2.8)	0.83	0.21-3.19	0.78
Referral for Infection (%)	50 (20.8)	12 (11.1)	0.47	0.24-0.93	0.03
Arrival SBP, mean mmHg (SD)	116 (31)	120 (32)	1.00	0.99-1.01	0.19
Arrival DBP, mean mmHg (SD)	66 (19)	66 (17)	1.00	0.99-1.01	0.94
Arrival MBP, mean mmHg (SD)	82 (22)	84 (20)	1.00	0.99-1.01	0.49
Arrival Hearth Rate, mean (SD)	102 (27)	95 (30)	0.99	0.98-0.99	0.016
Arrival SpO2, mean % (SD)	93 (8)	93 (7)	1.00	0.97-1.04	0.97
Arrival GCS, median (IQR)	15 (15-15)	15 (15-15)	0.89	0.81-0.99	0.048
Arrival Body Temperature, mean °C (SD)	37.7 (1.5)	36.9 (1.7)	0.75	0.65-0.87	<.001
Arrival qSOFA, mean (SD)	1.1 (0.8)	1.2 (0.8)	1.10	0.83-1.46	0.48
Pulmonary source of infection (%)	116 (48.3)	53 (49.1)	1.03	0.65-1.62	0.89
Urinary source of infection (%)	51 (21.3)	19 (17.6)	0.78	0.43-1.41	0.41
SST source of infection (%)	12 (5)	8 (7.4)	1.52	0.60-3.83	0.38
GI source of infection (%)	15 (6.3)	5 (4.6)	0.73	0.26-2.06	0.55
Biliary source of infection (%)	12 (5)	5 (4.6)	0.92	0.32-2.69	0.88

Tab. 6 (continued): Crude odds ratio for all cause death at day 28

Total, n = 348	28-day survivors n = 240	28-day non-survivors n = 108	OR	95% CI	*p*
Implicit presentation (%)	61 (25.4)	42 (38.9)	1.87	1.15-3.03	0.011
Identification of Infection Site (%)	231 (96.3)	100 (92.6)	0.49	0.18-1.29	0.14
Bacteremia (%)	80 (33.3)	37 (34.3)	1.04	0.64-1.69	0.87
Time to diagnosis, mean hours (SD)	8 (21)	8.5 (16)	1.00	1.00-1.00	0.79
Time to treatment, mean hours (SD)	10 (27)	10 (17)	1.00	1.00-1.00	0.79
Time to ICU, mean hours (SD)	40 (113)	32 (89)	1.00	1.00-1.00	0.57
Overall SOFA, mean (SD)	4.5 (2.7)	6.3 (3.6)	1.20	1.12-1.29	<.001
ABT to Pathogen Adequacy (%)	121 (50.4)	56 (51.8)	0.97	0.57-1.66	0.61

Tab. 7: Adjusted odds ratio for all cause death at day 28. aOR = adjusted Odds Ratio, CI = Confidence Interval

Covariate	aOR	95% CI	*p*
Implicit Presentation	2.14	1.24-3.68	0.006
Age	1.04	1.02-1.06	<.001
Arrival Body Temperature	0.80	0.68-0.95	0.007
Overall SOFA score at diagnosis	1.20	1.11-1.30	<.001

Fig. 1 : Study's flowchart. ED = Emergency Department, MICU = Medical Intensive Care Unit

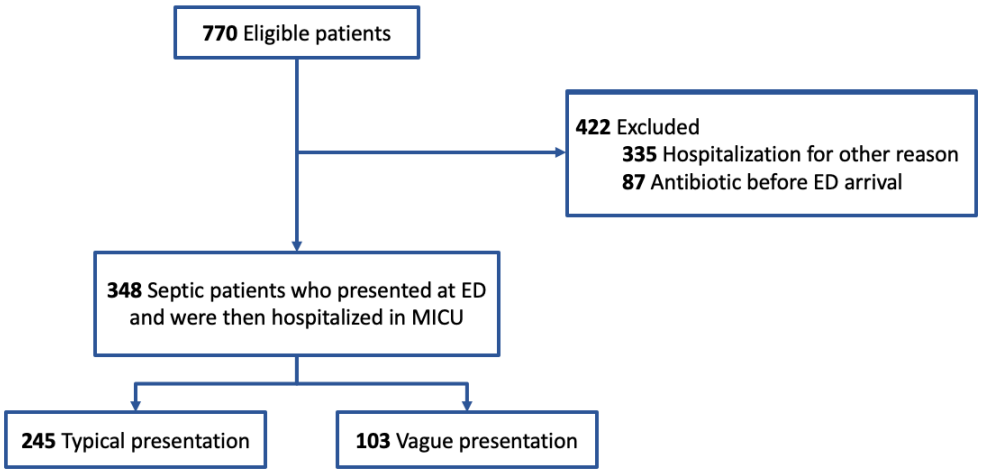


Fig. 2 : Kaplan-Meier survival analysis between the two groups

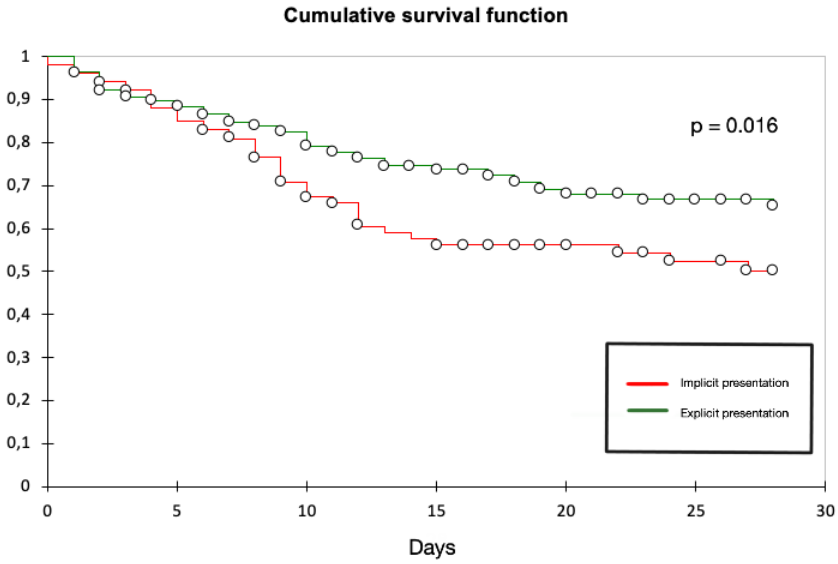
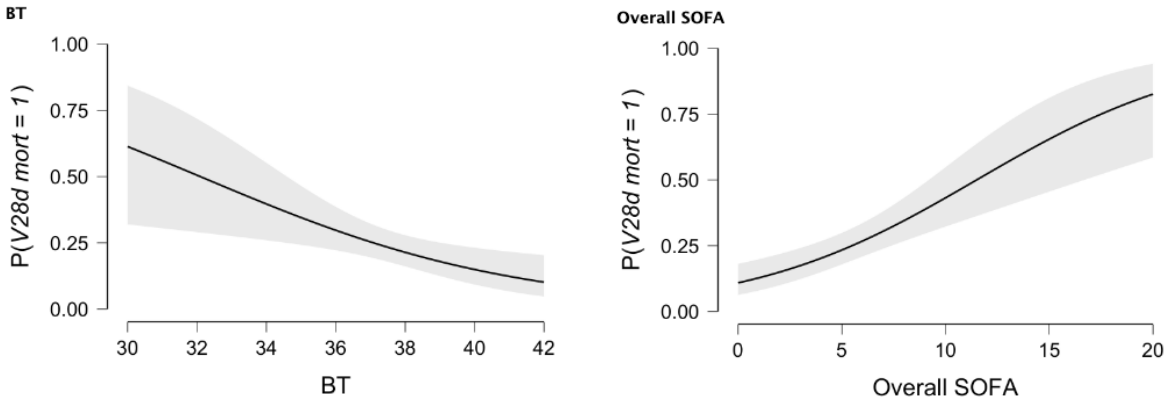


Fig. 3 : Multivariate analysis of Body Temperature (BT) and overall SOFA score at the time of diagnosis at ED presentation for 28-day mortality



Université de Bourgogne
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Circonscription

UNE PRESENTATION VAGUE AUGMENTE LA MORTALITE A 28 JOURS CHEZ LES PATIENTS SEPTIQUES

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Contexte : Le sepsis se définit comme une réponse immunitaire dysrégulée à l'infection susceptible de mettre rapidement en jeu le pronostic vital du patient. Son identification précoce est donc cruciale afin de réduire le délai de traitement. Cependant, la présentation clinique de l'infection chez ces patients peut parfois être trompeuse (présentation dite implicite ou vague), sans que l'on connaisse encore précisément l'impact et la signification de ce phénomène.

Méthodes : Une étude rétrospective, incluant tous les patients admis au Service d'Accueil des Urgences puis hospitalisés en Médecine Intensive Réanimation avec un diagnostic final de sepsis, a été conduite. En accord avec des critères publiés, deux groupes de patients septiques ont été identifiés selon leur présentation clinique aux urgences: présentation explicite ou présentation vague/implicite. Dans un premier temps, ces deux groupes ont été comparés selon les données de base, la sévérité clinique, les caractéristiques de l'infection, les modalités de prise en charge et le devenir des patients. Secondairement, l'impact d'une présentation vague sur la mortalité à 28 jours, a été étudié par analyse uni- puis multivariée en utilisant un modèle de régression logistique.

Résultats : parmi les 348 patients inclus dans la cohorte de l'étude, 103 (30%) avaient une présentation implicite aux Urgences. Ces patients présentaient davantage de comorbidités, mais étaient moins sévères à l'arrivée aux Urgences. En outre, le taux de bactériémie était plus bas chez ces patients. Cependant, la mortalité à 28 jours était plus élevée lorsque la présentation du sepsis était vague (40.8% vs. 26.9%, p = 0.011). ainsi que les délais de diagnostic, de mise en route de l'antibiothérapie et la durée d'hospitalisation. En analyse multivariée, une présentation clinique implicite du sepsis restait associée à un risque de décès plus élevé (odds ratio ajustée 2.14, 95% CI, 1.24-3.68, p = 0.06), au même titre que l'âge du patient, son score SOFA au moment du diagnostic et sa température. Par contre, les délais de diagnostic, de traitement et d'hospitalisation en Réanimation Médicale n'expliquaient pas la surmortalité.

Conclusions : Presque un tiers des patients septiques admis en réanimation avaient une présentation vague/implicite aux Urgences. Une telle présentation clinique du sepsis, malgré une sévérité apparente plus marquée, était un facteur de risque indépendant de mortalité à 28 jours, sans que les retards au diagnostic et à l'antibiothérapie qui en découlent ne puissent l'expliquer en totalité. Bien qu'il soit nécessaire de confirmer ces résultats, ils confirment le peu de données publiées à ce sujet, et incitent à mieux analyser ce sous-groupe de patients septiques, toujours exclus des essais cliniques, notamment en termes de réponse immune à l'infection.

MOTS-CLES : SEPSIS, INFECTION, PRESENTATION, SYMPTOMS, MORTALITY