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Diagnostic power of LIAISON MeMed BV® for bacterial infection in adult patients seen in Emergency Departments due to infections

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ABSTRACT

Objectives. To analyze the diagnostic accuracy of the new MeMed® test to predict bacterial infection in adult patients seen in emergency departments (ED) with clinical suspicion of infection, as well as to compare its performance with other commonly used biomarkers (protein C reactive-PCR-, procalcitonin -PCT-).

Methods. A prospective, observational and analytical study was carried out on adult patients who were treated in an ED with the clinical diagnosis of an infectious process. Follow-up was carried out for 30 days. The diagnosis of bacterial infection (BI) was considered as the dependent variable. The predictive ability was analyzed with the area under the curve (AUC) of the receiver operating characteristic (ROC) and the values of sensitivity (Se), specificity (Es), positive predictive value (PPV) and negative predictive value (NPV) of the PCR, PCT, leukocyte count and the LIAISON® MeMed® test.

Results. The study included 258 patients, 54 (15.6%) of whom died within 30 days of visiting the ED. The mean age was 68.28 (SD 19.53) years, 57.4% (148) were men. At 30 days, the group with the IB diagnosis had 137 patients, the viral infection group 68 cases and 17 in the indeterminate group. The AUC-ROC achieved by MeMed® in the group that analyzes all patients was 0.920 (95% CI: 0.877-0.962) and the PCT was 0.811 (95% CI: 0.754-0.867). With a cut-off point (PC) > 65 points of the MeMed® test, achieves a Se: 79.2% and Es: 91.2% and with PC > 90 points a Se: 57% and Es: 95.9%. Applying the Youden index, the PC > 50 points achieves Se:84.1% and Es:88.2%.

Conclusions. In adult patients treated with clinical suspicion of infection in the ED, the LIAISON MeMed® test has a great ability to diagnose its bacterial origin and achieves better performance than PCT, PCR and leukocyte count.

Keywords: Biomarkers, Emergency Department, Diagnostic, Bacterial Infection

Poder diagnóstico de infección bacteriana de LIAISON MeMed BV® en los pacientes adultos atendidos en urgencias por sospecha de infección

RESUMEN

Objetivos. Analizar la precisión diagnóstica de la nueva prueba MeMed® para predecir infección bacteriana en los pacientes adultos atendidos con sospecha clínica de infección en el servicio de urgencias hospitalario (SUH), así como comparar su rendimiento con otros biomarcadores de uso habitual (proteína C reactiva-PCR, procalcitonina -PCT-).

Métodos. Estudio observacional, de cohortes, prospectivo y analítico de pacientes adultos atendidos en un SUH con el diagnóstico clínico de un proceso infeccioso. Se realizó un seguimiento durante 30 días. Como variable dependiente se consideró el diagnóstico de infección bacteriana (IB). Se analizó la capacidad predictiva con el área bajo la curva (ABC) de la característica operativa del receptor (COR) y los valores de sensibilidad (Se), especificidad (Es), valor predictivo positivo (VPP) y negativo (VPN) de la PCR, PCT, recuento de leucocitos y el test LIAISON® MeMed®.

Resultados. Se incluyó a 258 pacientes, de los que 36 (14%) habían fallecido a los 30 días tras su consulta en el SUH. La edad media fue 68,28 (DE 19,53) años, el 57,4% (148) eran hombres. A los 30 días el grupo con el diagnóstico IB tenía 137 pacientes, el grupo infección viral 68 casos y 17 en el grupo indeterminado. El ABC-COR que consigue MeMed® en el grupo que analiza todos los pacientes es de 0,920 (IC 95%: 0,877-0,962) y la PCT de 0,811 (IC 95%: 0,754-0,867). Con un

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punto de corte (PC) > 65 puntos del test MeMed® se obtiene una Se:79,2% y Es:91,2% y con PC > 90 puntos una Se: 57% y Es:95,9%. Aplicando el índice de Youden el PC > 50 puntos consigue una Se:84,1% y Es:88,2%.

Conclusiones. En los pacientes adultos atendidos con sospecha clínica de infección en el SUH, la prueba de LIAISON MeMed® presenta una gran capacidad para diagnosticar su origen bacteriano y obtiene un mejor rendimiento que la PCT, la PCR y el recuento de leucocitos.

Palabras clave: Biomarcadores, Servicio de Urgencias, Diagnóstico, Infección bacteriana.

INTRODUCTION

The number of patients presenting with suspected infections to hospital Emergency Departments (ED) has significantly increased in recent years, now accounting for 15%-20% of all daily ED visits in Spain [1,2]. Moreover, the severity of clinical presentations and both in-hospital and short-term (30-day) mortality has risen, particularly among patients meeting sepsis criteria, those with significant comorbidities, immunocompromised individuals, the elderly, and those with confirmed bacteremia diagnosed in the ED [3,4].

In this context, early and appropriate administration of antibiotic (AB) treatment, combined with infection source control, as well as immediate diagnostic-therapeutic decisions (e.g., ordering additional tests, obtaining blood cultures and other microbiological samples, determining the level of hemodynamic support needed, and deciding on hospital admission), has a direct impact on the survival of patients with severe bacterial infections [1,2,5,6].

However, clinical presentation of acute infections is often non-specific and variable, complicating timely identification of these patients and determining whether the underlying etiology is bacterial or viral [1,2]. As a result, antibiotics are often unnecessarily prescribed without confirmation of bacterial pathogen, particularly in patients presenting with febrile illness of unknown origin. In 30%-50% of these cases, the cause is non-infectious. Excessive use of antibiotics contributes to increased antibiotic resistance and bacterial virulence [2,7,8]. Conversely, delayed antibiotic administration in cases of bacterial infections can have similarly adverse outcomes. This reality highlights a critical challenge: increased diagnostic testing, prolonged hospital stays, elevated healthcare costs, and, in some instances, unnecessary or delayed treatments [1,2,7,8].

In recent years, there has been a growing focus on developing objective tools to aid in predicting, from the initial assessment of the patient with a suspected serious infection, the diagnosis, prognosis, severity, and the likelihood of bacterial etiology or bacteremia— factors that are crucial in determining patient outcomes and mortality in infectious diseases [2,5,8-11]. Inflammatory and infection biomarkers (IRIB) have emerged as essential tools for clinicians to enhance the diagnosis and management of infections, as they provide timely information to guide critical decisions in the ED [2,5,8-12]. Among these biomarkers, procalcitonin (PCT) stands out as a sensitive and specific indicator of bacterial infection, offering insights into the causative infectious etiology, the clinical progression (e.g., progression to severe sepsis or septic shock), and associated mortality [2,9,10,12].

Recently, a novel diagnostic test based on altered concentrations of specific immune response proteins has showns significant promise. This test, known as LIAISON® MeMed® BV, calculates a diagnostic score using a model that integrates the levels of three host-derived soluble proteins, enabling differentiation between bacterial and viral infection [13,14]. To date, relatively few studies have evaluated the predictive ability of the LIAISON® MeMed® BV test in detecting bacterial infections, with most prior studies focusing on pediatric populations [15-20], and few included adult patients [21-27]. This is the first host-response diagnostic test to incorporate a combination of three circulating proteins in blood into a predictive score with each protein displaying complementary dynamics in viral and bacterial infections [13-27]: 1- Tumour necrosis factor-related apoptosis-inducing ligand (TRAIL): elevated in viral infections and decreased in bacterial infections, 2 - Interferon gamma-induced protein 10 (IP-10): significantly increased in viral infections and to a lesser extent in bacterial infections, and 3 - C-reactive protein (CRP): exhibiting an inverse pattern to IP-10. The inclusion of unrelated host proteins, which act through different biological pathways, enhances diagnostic precision. In particular, the integration of host proteins that are upregulated in viral infections provides an innovative complement to bacterial-induced proteins like CRP or PCT, which are already widely used in clinical practice [13-27].

The primary objective of this study is to evaluate the diagnostic accuracy of the LIAISON MeMed® BV test in predicting bacterial infections in adult patients presenting to the ED with clinical suspicion of an acute infection, and to compare its performance with other commonly used biomarkers, such as CRP and PCT.

PATIENTS AND METHODS

Design and setting. A prospective, observational cohort study was conducted involving adult patients (aged 18 years or older) who presented to our ED with a clinical diagnosis of an acute infection. Patients were followed up for 30 days, and the diagnosis of infection was confirmed after this period. The study was conducted in a tertiary university hospital with 786 beds, affiliated with the Castilla-La Mancha Health Service.

Study period and population. Between July 1st 2023, and February 7th, 2024, patients aged 18 years or older, clinically diagnosed with an acute infection in the ED were included in the study using convenience sampling (based on the availability of the study investigators). For these

Table 1 **Interpretation of the LIAISON® MeMed® BV score results**

MeMed® Score	Interpretation
0 to 10	High likelihood of VI (or other non-bacterial aetiology)
11 to 34	Moderate likelihood of VI (or other non-bacterial aetiology)
35 to 65	Equivocal
66 to 89	Moderate likelihood of BI (or VI-BI co-infection)
90-100	High likelihood of BI (or VI-BI co-infection)

VI: viral infection; BI: bacterial infection. Adapted from the manufacturer's guidelines and references 13, 21, and 22.

patients, attending physicians, guided by clinical and epidemiological characteristics, requested blood samples for complementary laboratory analyses, including blood count, biochemistry, and inflammatory biomarkers such as CRP, PCT, serum lactate, and the LIAISON® MeMed® BV test. Additional microbiological diagnostic tests, such as blood cultures, other cultures, rapid tests, serology, and antigenuria, were also performed as needed.

Pediatric patients and patients from obstetrics and gynecology wards were excluded.

Collected variables. The diagnosis of bacterial infection (BI) was considered the dependent variable. Patients were classified into the following groups based on the confirmation of suspected diagnosis within 30 days:1. – BI, microbiologically confirmed: diagnosis suspected in the ED and confirmed through complimentary testing; 2.- Viral infection (VI), microbiologically confirmed: diagnosis suspected in the ED and confirmed through complimentary testing; 3.- BI, not microbiologically confirmed: diagnosis suspected in the ED without microbiological confirmation at 30 days post presentation. This diagnosis required unanimous agreement by a group of physicians, including an emergency physician, a microbiologist, a clinical analysis laboratory specialist, and an internist); 4.- VI, not microbiologically confirmed: diagnosis suspected in the ED without microbiological confirmation at 30 days post presentation with unanimous agreement among physicians.; 5.- Undetermined suspicion: cases where the follow-up group did not reach consensus on infectious etiology diagnosis.

The following variables were collected based on their potential influence on prognosis and patient outcomes during the 30 days post-ED visit: A.- Demographic and epidemiological variables: age, sex, institutionalization, prior AB use, hospitalization within the last month, Charlson comorbidity Index [28].B.- Clinical variables: temperature, altered consciousness defined as ≤14 points on the Glasgow Coma Scale, presence of nausea/vomiting, chills/shivering, systolic blood pressure (SBP), sepsis criteria and its defining variables according to the 2001 Sepsis Consensus Conference (sepsis defined with a qSOFA score ≥2), and septic shock with its defining variables as outlined by the Sepsis-3 conference [1]. Prognostic and outcome variables: time since symptom onset, hospital length of stay, patient disposition, ED re-consultation or readmission, and 30-day mortality post-ED visit. D. Biochemical laboratory variables: routine blood-work and determination of biomarkers (CRP in mg/L, PCT in ng/ml, serum lactate in mmol/L); and E. Microbiological variables: any data provided by the microbiology service.

Definitions, techniques, and established sample methods. The LIAISON® MeMed BV® test employs a decision algorithm that integrates the blood concentration levels of three immune system proteins, generating a qualitative numerical score, ranging from 0 to 100 points, indicating the likelihood of a bacterial immune response or bacterial co-infection versus a probable viral immune response. The test utilizes chemiluminescence immunoassay (CLIA) technology to measure the three proteins (TRAIL 15-300 pg/ml, IP-10 100-2000 pg/ml and CRP 1-250 mg/l). The diagnostic accuracy for identification of BI was evaluated first across the entire patient cohort and then in specific subgroups, including patients microbiologically confirmed diagnoses, those 65 years or older, and those diagnosed with lower respiratory tract infections (LRTI). Additionally, following the manufacturer's (DiaSorin) recommendations and to account for potential artifacts or uncontrolled immune responses, comparisons were performed excluding patients who met the LIAISON-MeMed BV® test exclusion criteria ("LIAISON-MeMed exclusion group"). These exclusion criteria included: documented symptoms and fever lasting more than 7 days, suspected gastroenteritis/colitis, active inflammatory disease, congenital or acquired immunodeficiency, HIV, HBV, HCV, active tuberculosis, chronic fungal or parasitic infections, pregnancy, active malignancy, those with significant trauma, major burns, or recent major surgery within the last 7 days.

The interpretation of LIAISON® MeMed BV® results was initially based on the manufacturer's recommendations and early published studies [13, 21, 22] (Table 1).

For IRIB, reference values from our laboratory were utilized. PCT was measured by CLIA on the cobas e801 sys-

Table 2 Microbiological test performed

Two sets of blood culture samples, each consisting of two culture bottles (BD BACTEC™™ Plus Aerobic and Lytic Anaerobic media), were incubated for 5 days in the Becton Dickinson BACTEC system. For cases with suspected endocarditis, incubation was extended up to 30 days.
Multiple PCR analysis using the Biomérieux FilmArray® system was employed for the detection of bacteria, viruses, yeasts, and parasites through various
Aerobic/anaerobic and fungal microbiological studies of upper and lower respiratory tract samples were conducted with an incubation period of 3-5 days.
Urine antigen testing for S. pneumoniae y L. pneumophila (serogroup 1) was performed using the SSI Diagnostica ImmuView® lateral flow immuno-
Respiratory virus detection (**SARS-CoV-2**, *, influenza A, influenza B, and respiratory syncytial virus) was carried out on nasopharyngeal swab samples using real-time PCR systems Diasorin LIAISON MDX, Cepheid and Vircell GeneXpert, analysed on the Werfen CFX96 system.
Serological tests were performed to detect pathogens involved in respiratory infections. Detection of IgG/IgM classes was achieved using a chemiluminescent immunoassay technique on the Virclia system (Vircell).
Aerobic and fungal microbiological studies of urine samples were conducted with an incubation period of 24-48 hours.
Aerobic/anaerobic and fungal microbiological studies of skin and soft tissue samples, sterile fluids, and other exudates were conducted with an incubation
Microbiological studies of gastrointestinal tract samples were carried out with an incubation period of 2-5 days.
Micro-organisms in microbiological studies were identified using BrukerDaltonics MALDI-TOF mass spectrometry.
Antigen detection of *Clostridioides difficile* GDH in stool samples was performed using the qualitative enzyme immunoassay Immunocard® C. difficile GDH by Meridian Bioscience, with confirmation of toxigenic strains through LAMP methodology on the Meridian Bioscience Illumipro-
Markers related to other viral infections (e.g., hepatitis viruses, HIV) were determined using a chemiluminescent immunoassay technique on the Alinity system (Abbott).
Detection of mycobacteria Ziehl-Neelsen staining and culture in MGIT liquid medium (Becton Dickinson) was performed, with incubation in the MG T960 system (Becton Dickinson®) for 40 days and in solid Lowenstein medium for an incubation period of 60 days. Mycobacteria were identified using BrukerDaltonics MALDI-TOF mass spectrometry. PCR for *Mycobacterium tuberculosis* was conducted directly on samples using the GeneXpert

tem (Roche), with lithium heparin plasma, and a detection range of 0.02–100 ng/ml. Lactate: measured using amperometry on the Gem 5000 gasometer (Werfen®), with whole blood with lithium heparin, and a detection range of 0.3–17 mmol/L (3–153 mg/dl). CRP: measured by immuno-turbidimetry on the cobas c702 system (Roche), with lithium heparin plasma, and a detection range of 0.6–305 mg/l.

The microbiological tests performed are summarized in Table 2, which lists those used to confirm bacterial or viral etiology. Blood cultures were performed on all patients, in accordance with institutional protocols as they were deemed to have a potential severe infection. Additionally, one or more of the microbiological tests listed in Table 2 were conducted based on the diagnostic suspicion determined by the attending ED physician.

Blood cultures (BC) were collected using the standard venipuncture technique. For each patient, two separate extractions were performed, spaced over time and drawn from different venipuncture sites to ensure reliability. The procedure for extraction, inoculation timing, and definitions of true bacteremia and contaminated blood cultures followed the protocols established in a recent study by the INFURG-SEMES group [29].

Statistical analysis. The association between BI and independent variables was analyzed using means and standard deviations (SD) for quantitative variables, and percentages for qualitative variables. Depending on the nature of the data, the Chi-square or Fisher's exact test, Student's t-test, and Mann-Whitney's U test were applied to assess the relationship between BI diagnosis and independent variables, including dichotomized variables. A p value <0.05 was considered statistically significant, and all tests were two-tailed.

A descriptive analysis (absolute numbers and percentages) was performed for both patient groups, categorized based on the final diagnosis as BI or VI.

The predictive accuracy of BI at 30 days for various IRIB, leukocyte counts, and the LIAISON® MeMed BV® test was assessed using receiver operating characteristic (ROC) curve analysis. This included calculating the area under the curve (AUC) with a 95% confidence interval (CI) and comparing it to the neutral value (0.5). Standard errors for the AUC values were determined using non-parametric methods.

Cut-off points (CP) for IRIB values were determined based on recent publications from the INFURG-SEMES group [9,10]. For the LIAISON® MeMed BV® test, CP values were established according to manufacturer's recommendations and prior studies [13-25]. Additionally, the CP with the highest diagnostic accuracy for the LIAISON® MeMed BV® test was identified using the Youden index, which maximizes the difference between true positive and false positive rates. Sensitivity (Se), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV), and

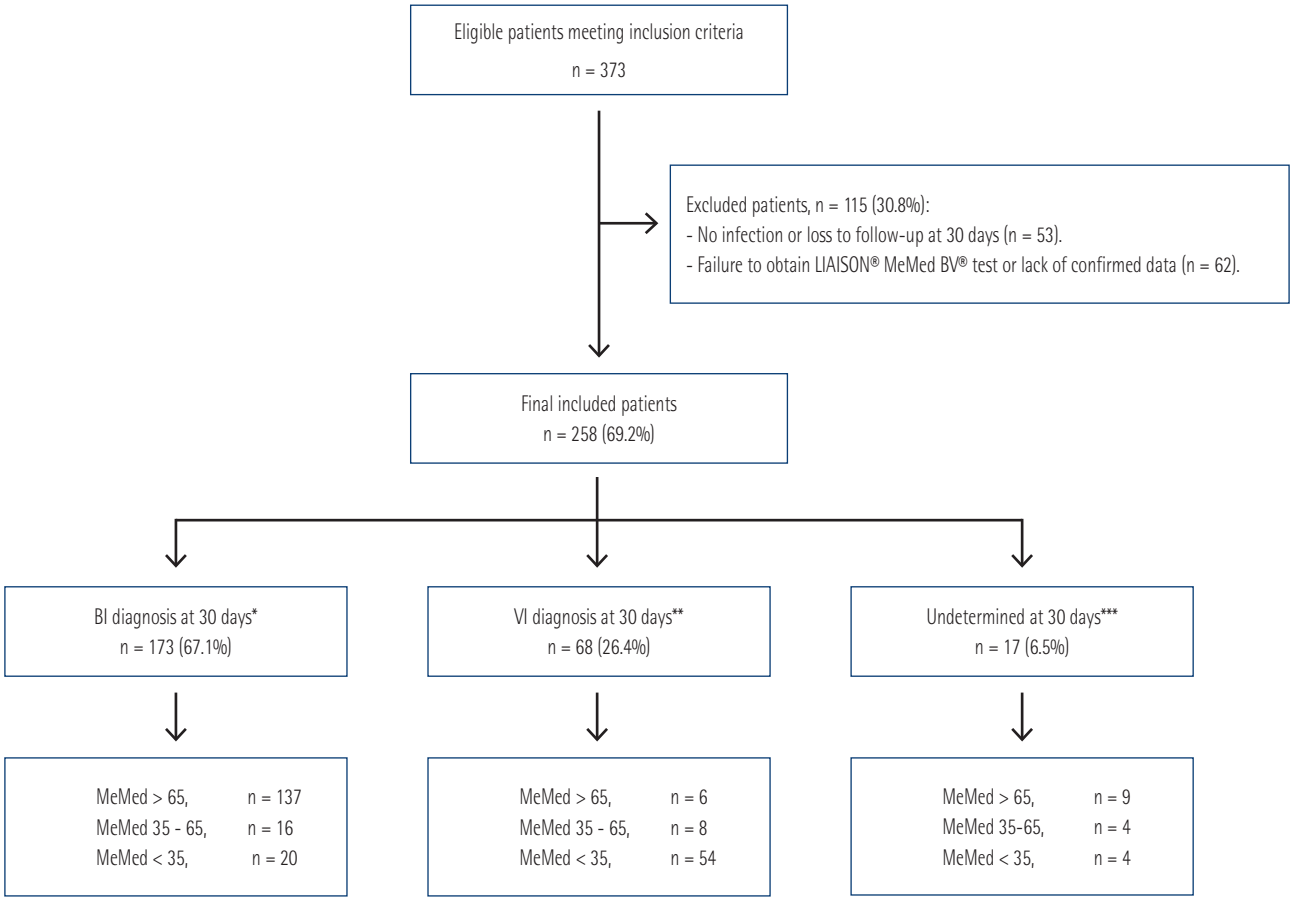

Figure 1 | **Flowchart of case inclusion**

BI: bacterial infection; VI: viral infection

***: Includes patients with micro-biologically confirmed BI diagnosis and those with BI suspicion in the ED that was maintained at 30 days (by consensus of a group composed of an emergency physician, a microbiologist, a clinical laboratory specialist, and an internist).**

****: Includes patients with micro-biologically confirmed VI diagnosis and those with VI suspicion in the ED that was maintained at 30 days (by consensus of the evaluative group described above).**

*****: Patients with suspected BI or VI diagnosis in the ED without microbiological confirmation, where the evaluative group did not reach a unanimous consensus or raised the possibility of co-infection (BI + VI).**

positive (LR+) and negative (LR–) likelihood ratios were calculated.

For each outcome studied, the CP results were calculated with their corresponding 95%CI using exact binomial and Taylor methods. Statistical analyses were performed using IBM-SPSS® Statistics 29 for Windows and STATA 17.0. Ethical considerations. The study adhered to all institutional and international ethical protocols and standards, including the Declaration of Helsinki, to ensure the appropriate use of patient data. All patient data were coded to maintain confidentiality. Electronic medical and primary care records were reviewed as needed.

The study was approved by the Clinical Research Ethics Committee with medicinal products (CEIm) of the University Hospital of Toledo (No. 1075/2023). Patients or their families received both oral and written information about the study, and prior informed consent was obtained before inclusion. The study involved no therapeutic interventions or clinical implications.

RESULTS

During the study period, 373 patients met the initial inclusion criteria through convenience sampling. Of these,

Table 3 **Clinical-epidemiological, comorbidity, evolution and analytical characteristics studied during the initial evaluation of patients in the ED (univariate analysis)**

	Total n=258	Undetermined diagnosis n=17 (6.5%)	Bacterial infection diagnosis n= 173 (67.1%)	Viral infection diagnosis n= 68 (26.4%)	p-value*
DEMOGRAPHIC-EPIDEMIOLOGICAL DATA					
Age (years), mean (SD)	68.28 (19.53)	70.47 (17.05)	69.03 (19.33)	65.79 (20.61)	0.252
Age >65 years, (%)	162 (62.8)	10 (58.8)	112 (64.7)	40 (58.8)	0.652
Male gender, (%)	148 (57.4)	10 (58.8)	99 (57.2)	39 (57.4)	0.952
Institutionalized, (%)	42 (16.3)	4 (23.5)	29 (16.8)	9 (13.2)	0.302
Use of AB in the previous month, (%)	101 (39.1)	8 (47.1)	66 (38.2)	27 (39.7)	0.768
Hospitalization in the previous month, (%)	48 (18.6)	3 (17.6)	31 (17.9)	14 (20.6)	0.654
COMORBIDITIES					
Charlson index[a] [mean (SD)]	4.78 (3.16)	5.65 (3.98)	4.83 (3.15)	4.83 (3.15)	0.352
Charlson index ≥ 3, (%)	188 (72.86)	13 (76.47)	129 (74.56)	129 (74.56)	0.084
CLINICAL AND SEVERITY DATA					
Temperature in degrees Celsius [mean (SD)]	36.86 (0.94)	36.42 (0.56)	36.80 (0.81)	37.13 (1.23)	**0.015**
Temperature > 38,3°C, (%)	25 (9.7)	1 (5.9)	15 (8.7)	9 (13.2)	0.233
HR in bpm [mean (SD)]	96.22 (21.24)	95.47 (17.77)	97.67 (21.76)	93.96 (20.50)	0.216
HR > 90 bpm, (%)	153 (59.3)	7 (41.2)	108 (62.4)	38 (55.9)	0.188
RR in rpm [mean (SD)]	23.59 (6.5)	24.14 (6.46)	23.86 (6.70)	22.85 (6.30)	0.417
RR ≥ 22 rpm, (%)	145 (56.6)	11 (68.8)	94 (54.7)	40 (58.8)	0.505
Altered consciousness ECG ≤ 14, (%)	69 (19.9)	2 (0.6)	41 (14.0)	28 (51.9)	**0.008**
SBP in mmHg [mean (SD)]	118.66 (27.06)	121.18 (32.64)	115.76 (26.28)	125.41 (26.70)	**0.011**
SBP < 100 mmHg, (%)	75 (29.1)	5 (29.4)	57 (32.9)	13 (19.1)	0.083
Sepsis criteria (SIRS ≥ 2), (%)	167 (64.7)	7 (41.2)	123 (71.1)	37 (54.4)	**0.006**
qSOFA ≥ 2, (%)	72 (27.9)	6 (35.3)	56 (32.4)	10 (14.7)	**0.018**
Criteria Septic shock (Sepsis-3), (%)	17 (6.6)	1 (5.9)	16 (9.2)	0 (0.0)	**0.004**
Nausea/vomiting, (%)	57 (22.1)	8 (47.1)	38 (22.0)	11 (16.2)	**0.023**
Chills/shivering, (%)	108 (41.9)	4 (23.5)	73 (42.2)	31 (45.6)	0.254
EVOLUTION AND OUTCOME DATA					
Days since symptom onset [mean (SD)]	3.55 (3.23)	3.88 (3.60)	3.65 (3.36)	3.22 (2.79)	0.348
Initial patient disposition					**<0.001**
Discharge	53 (20.5)	5 (29.4)	17 (9.8)	31 (45.6)	
Observation/Short-Stay Unit	26 (10.1)	1 (5.9)	16 (9.2)	9 (13.2)	
Conventional hospitalization ward	152 (58.9)	9 (52.9)	116 (67.1)	27 (39.7)	
Intensive care unit	16 (6.2)	1 (5.9)	14 (8.1)	1 (1.5)	
Operating theatre	10 (3.9)	1 (5.9)	9 (5.2)	0 (0.0)	
Exitus in ED	1 (0.4)	0 (0.0)	1 (0.6)	0 (0.0)	
Readmission within 30 days after ED care, n (%)	33 (12.8)	4 (23.5)	21 (12.4)	8 (11.8)	0.729
Hospital length of stay in days [mean (SD)]	7.72 (8.47)	10.71 (18.64)	8.65 (7.37)	4.60 (6.18)	**<0.001**
Mortality within 30 days after ED care	36 (14.0)	3 (17.6)	28 (16.2)	5 (7.4)	**0.048**
ANALYTICAL AND MICROBIOLOGICAL FINDINGS					
True bacteremia[b], n (%)	47 (18.2)	2 (11.7)	45 (26.1)	0 (0.0)	**<0.001**
Creatinin in mg/dl [mean (SD)]	1.38 (1.04)	1.52 (1.41)	1.47 (1.14)	1.13 (0.54)	**0.023**
Leukocytes per mm^3 [mean (SD)]	12.603 (6.544)	12.606 (7.886)	14.112 (6.662)	8.538 (3.795)	**<0.001**
Neutrophils (% of leucocytes) [mean (SD)]	80.22 (14.03)	72.80 (21.15)	82.21 (13.79)	77.01 (11.21)	**0.006**
Monocytes (% of leukocytes) [mean (SD)]	7.34 (5.48)	9.81 (11.55)	6.57 (4.91)	8.68 (4.10)	**0.002**
Lymphocytes (% of leukocytes) [mean (SD)]	11.50 (11.28)	15.15 (11.87)	10.49 (12.05)	13.16 (8.53)	**0.096**
Platelets per mm^3 [mean (SD)]	230.291 (101.369)	240.118 (108.662)	241.486 (105.615)	199.353 (81.623)	**0.003**
Serum lactate in mmol/l [mean (SD)]	19.34 (14.24)	19.46 (17.40)	20.52 (15.17)	15.18 (7.62)	**0.029**
C-reactive protein in mg/L [mean (SD)]	118.6 (116.6)	79.8 (102.3)	152.1 (122.2)	43.2 (48.1)	**<0.001**
Procalcitonin in ng/ml [mean (SD)]	4.14 (13.40)	0.86 (1.73)	5.84 (16.01)	0.57 (2.23)	**<0.001**
Procalcitonin ≥ 0,25 ng/ml, n (%)	137 (54.6)	7 (43.8)	116 (68.6)	14 (21.2)	**<0.001**
Procalcitonin ≥ 0,5 ng/ml, n (%)	106 (42.4)	5 (31.3)	94 (55.6)	7 (10.6)	**<0.001**
MeMed BV® score [mean (SD)]	62 (39)	65 (35)	79 (29)	18 (27)	**<0.001**
MeMed BV® < 35, n (%)	78 (30.23)	4 (23.52)	20 (11.56)	54 (79.41)	**<0.001**
MeMed BV® 35 - 65, n (%)	28 (10.85)	4 (23.52)	16 (9.24)	8 (11.76)	**<0.001**
MeMed BV® > 65, n (%)	152 (58.91)	9 (52.94)	137 (79.19)	6 (8.82)	**<0.001**

ED: emergency department; SD: standard deviation; n: number of cases; AB: antibiotics; C: Celsius; HR: heart rate; bpm: beats per minute; RR: respiratory rate; rpm: respirations per minute; max: maximum; GCS: Glasgow Coma Scale; SBP: systolic blood pressure; SIRS: systemic inflammatory response syndrome; qSOFA: quick Sepsis-related Organ Failure Assessment. *Two-tailed comparison between bacterial infection and viral infection groups. [a]Charlson Comorbidity Index: age-adjusted (reference 28). [b]True bacteremia: defined according to criteria from previous INFURG-SEMES studies (reference 29). Sepsis criteria (SIRS ≥ 2) based on

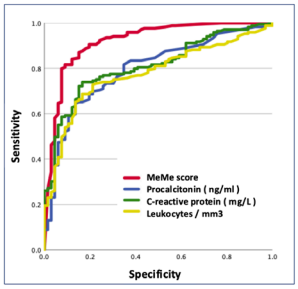

Figure 2a	AUC-ROC (95%CI)	p
MeMed® (score)	0.920 (0.877-0.962)	< 0.001
Procalcitonin (ng/ml)	0.811 (0.754-0.867)	< 0.001
CRP (mg/L)	0.796 (0.735-0.857)	< 0.001
Leukocytes (mm3)	0.778 (0.717-0.839)	< 0.001

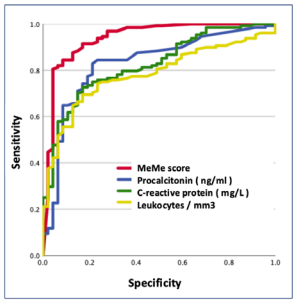

Figure 2b	AUC-ROC (95%CI)	p
MeMed® (score)	0.938 (0.892-0.984)	< 0.001
Procalcitonin (ng/ml)	0.829 (0.758-0.900)	< 0.001
CRP (mg/L)	0.824 (0.759-0.888)	< 0.001
Leukocytes (mm3)	0.782 (0.713-0.851	< 0.001

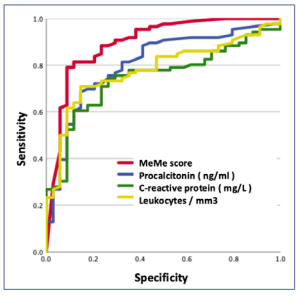

Figure 2c	AUC-ROC (IC 95%)	p
MeMed® (score)	0.896 (0.827-0.964)	< 0.001
Procalcitonin (ng/ml)	0.806 (0.721-0.892)	< 0.001
CRP (mg/L)	0.747 (0.657-0.837)	< 0.001
Leukocytes (mm3)	0.780 (0.695-0.865	< 0.001

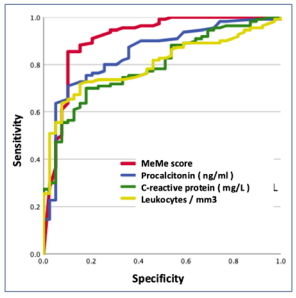

Figure 2d	AUC-ROC (95%CI)	p
MeMed® (score)	0.910 (0.847-0.972)	< 0.001
Procalcitonin (ng/ml)	0.847 (0.776-0.917)	< 0.001
CRP (mg/L)	0.792 (0.717-0.868)	< 0.001
Leukocytes (mm3)	0.800 (0.729-0.871	< 0.001

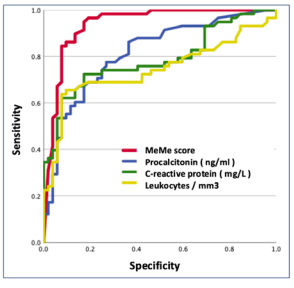

Figure 2e	AUC-ROC (95%CI)	p
MeMed® (score)	0.938 (0.891-0.986)	< 0.001
Procalcitonin (ng/ml)	0.815 (0.735-0.895)	< 0.001
CRP (mg/L)	0.787 (0.701-0.873)	< 0.001
Leukocytes (mm3)	0.744 (0.647-0.840)	< 0.001

Figure 2 | **Diagnostic capacity for bacterial infection in patients treated in the ED for infection**

2a: all patients; 2b: LIAISON-MeMed exclusion group; 2c: microbiological confirmation group; 2d: patients ≥ 65 years old; 2e: patients with lower respiratory tract infection. The p value indicates the risk of Type I error in testing the null hypothesis that the AUC-ROC is equal to 0.5. AUC-ROC: area under the receiver operating characteristic curve; 95% CI: 95% confidence interval; CRP: C-reactive protein.

Table 4 Possible clinical foci/diagnoses in the ED in the groups according to etiological suspicion

Clinical focus/diagnosis in the Emergency Department	Total n = 258	Undetermined diagnosis n=17 (6.5%)	Bacterial infection diagnosis n= 173 (67.1%)	Viral infection diagnosis n= 68 (26.4%)
Lower respiratory tract infection, n (%)	115 (44.6)	4 (23.5)	58 (33.5)	53 (77.9)
Urinary tract infection, n (%)	60 (23.3)	4 (23.5)	56 (32.4)	0 (0.0)
Abdominal infection[a],n (%)	34 (13.2)	1 (5.9)	28 (16.2)	5 (7.3)
Fever or suspected infection of unknown origin, n (%)	29 (11.2)	3 (17.6)	20 (11.6)	6 (8.8)
Skin and soft tissue infection, n (%)	14 (5.4)	4 (23.5)	6 (3.5)	4 (5.9)
Other foci[b], n (%)	6 (2.3)	1 (5.9)	5 (2.9)	0 (0.0)

[a]Gastroenteritis, infectious colitis, cholangitis or cholecystitis, hepatitis, appendicitis, etc.

[b]Otorhinolaryngology, suspected endocarditis, infection of vascular devices, etc.

115 (30.8%) were excluded due to loss to follow-up at 30 days, or due to non-infectious diagnosis, or failure to obtain a valid LIAISON® MeMed BV® result.

A total of 258 patients were included (Figure 1). Among these, 36 patients (14.0%) died within 30 days after their ED visit. The mean age was 68.28 (SD 19.53) years, 57.4% (148) were men.

Demographic, epidemiological, and comorbidity characteristics, as well as clinical data (signs and symptoms), severity, disposition, 30-day outcomes, analytical test results, blood culture results, and LIAISON® MeMed BV® test results are summarized in Table 3.

Significant differences were observed when comparing patients with a final diagnosis of BI versus all other patients in the following variables: temperature, altered level of consciousness, SBP <100 mmHg, qSOFA ≥2, SIRS ≥2, septic shock criteria (Sepsis-3), presence of nausea/vomiting, patient disposition, hospital length of stay, 30-day mortality, true bacteremia, and various laboratory results, including creatinine ≥2 mg/dl, lactatemia, platelet count, leukocyte count and proportions of monocytes and neutrophils, as well as CRP, PCT concentrations (dichotomized for ≥0.25 and ≥0.5 ng/ml), and LIAISON® MeMed BV® scores (dichotomized for <35, 35–65, and >65). In 45 (26.1%) of BI cases and 2 (11.7%) of the undetermined group, significant isolates were obtained from blood cultures.

The presumed clinical infectious focus in ED patients with a final diagnosis of BI or VI at 30 days is summarized in Table 4.

Figure 2 illustrates the AUC-ROC values for the leukocyte count, the studied IRIB (CRP, PCT), and the LIAISON® MeMed BV® test for diagnosing BI in the entire patient cohort (Figure 2a), as well as in the LIAISON® MeMed BV® test exclusion group (n = 237; Figure 2b), in patients with a microbiological confirmation (n = 155; Figure 2c), in elderly (≥65 years of age) patients (n= 162; Figure 2d), and in patients with lower respiratory tract infections (LRTI), including pneumonias, exacerbated COPD, and bronchitis) (n = 115; Figure 2e). For the group with true bacteremia (n = 47), the AUC-ROC was 0.936 (0.859–1.000), p <0.001.

Across all groups (Figure 2a-e), the LIAISON® MeMed BV® test achieved the highest diagnostic accuracy, followed by PCT. The LIAISON® MeMed BV® test AUC-ROC was 0.920 (95% CI: 0.877-0.962), and the PCT was 0.811 (95% CI: 0.754-0.867), for the entire patient cohort. Diagnostic accuracy values for predefined LIAISON® MeMed BV® test cut-off points and those identified by the Youden index, as well as for PCT, are presented in table 5.

Additionally, the diagnostic accuracy of PCT, CRP, and the LIAISON® MeMed BV® test were compared for the group of 28 patients with inconclusive results (i.e., LIAISON® MeMed BV® test score range 35–65). No significant results were observed: For PCT, an AUC-ROC of 0.622 (95% CI: 0.376–0.869), p = 0.371; for CRP, an AUC of 0.469 (95% CI: 0.210-0.729), p = 0.823; and for MeMed®, an AUC-ROC of 0.500 (95% CI: 0.213-0.787), p=1.

DISCUSSION

The results of this study confirm the high diagnostic accuracy of IRIBs, such as PCT [9,10,12], and particularly the new LIAISON® MeMed BV® test, in diagnosing bacterial infections among patients treated in the ED with suspected acute infection [13-26]. The LIAISON® MeMed BV® test is an innovative diagnostic test that achieved the highest accuracy for differentiating bacterial from viral infection and from those patients which are non-infectious [13,14]. Our findings align with previous studies, which demonstrated the utility of the test in adult patients [21-27], as well as pediatric patients [15-20].

The LIAISON® MeMed BV® is the first diagnostic test that integrates the concentration of three circulating blood proteins (derived from a mathematical formula generated

Table 5 Cut-off points and diagnostic performance for bacterial infection

All patients n = 258	AUC-ROC (95%CI)	Se % (95%CI)	Sp % (95%CI)	PPV % (95%CI)	NPV % (95%CI)	LR+ (95%CI)	LR- (95%CI)
MeMed BV score > 65	0.857 (0.803-0.911)	79.2 (72.2-84.8)	91.2 (81.1-96.49)	95.8 (90.7-98.3)	63.3 (52.9-72.6)	8.97 (4.21-19.32)	0.23 (0.17-0.31)
MeMed BV score > 90	0.801 (0.741-0.861)	57.0 (49.3-64.5)	95.9 (87.2-99.2)	97.4 (91.3-99.5)	46.8 (38.4-55.4)	13.24 (4.61-39.42)	0.45 (0.38-0.54)
MeMed BV score > 50*	0.852 (0.797-0.907	84.1 (77.4-89.3)	88.2 (77.6-94.4)	94.7 (89.4-97.5)	65.9 (55.2-75.3)	6.98 (3.63-13.43)	0.20 (0.15-0.28)
Procalcitonin ≥ 0.25 ng/ml	0.787 (0.707-0.858)	70.7 (62.9-77.4)	80.8 (68.7-89.6)	91.2 (84.3-95.8)	51.5 (41.7-61.4)	3.24 (2.01-5.21)	0.40 (0.31-0.51)
Procalcitonin ≥ 0.50 ng/ml	0.725 (0.659-0.791)	57.6 (49.8-65.2)	89.4 (78.8-95.3)	93.1 (85.8-96.9)	46.1 (37.6-54.9)	5.44 (2.77-10.9)	0.50 (0.41-0.60)

***Cut-off point obtained by the Youden index.**

Se: sensitivity; Sp: specificity; PPV: positive predictive value; NPV: negative predictive value; LR+: positive likelihood ratio; LR−: negative likelihood ratio; 95%CI: 95% confidence interval.

by a regression model) into a 0-100 score. IRIBs are induced by both viruses and bacteria [13-27]: TRAIL, increases in viral infections but decreases in bacterial infections, while IP-10 shows a greater increase in viral than bacterial infections. CRP, on the other hand, follows the opposite trend to IP-10 [13,14]. The synergy of the three IRIB significantly enhances the diagnostic accuracy compared to each individual biomarker [12].

The LIAISON® MeMed BV® test could serve as a novel tool in patients with suspected acute infections presenting with non-specific clinical findings, aiding in the early identification of bacterial or viral etiology [1,2] and improving appropriate antibiotic use in the ED, particularly for the most vulnerable [2,5,30]. The test can be readily integrated with other urgent laboratory analyses (and other IRIBs) using automated immunoassay devices [13-15]. Based on data In Spain, the estimated cost of the test ranges from €30–40 (as reported by the laboratory / manufacturer), depending on whether it is performed individually or with other urgent tests. Cost-effectiveness studies are needed to evaluate its potential to improve appropriate antibiotic use and optimize patient disposition.

Across all patients, the LIAISON® MeMed BV® test achieved an AUC-ROC of 0.920, which was similar to the exclusion group (as defined by the manufacturer) with an AUC-ROC of 0.938, and similar to patients with an LRTI, also with an AUC-ROC of 0.938. Slightly lower performance was observed in patients aged ≥65 years (AUC-ROC: 0.910) and those with a microbiological confirmation (AUC-ROC: 0.896), although these values remain high. The study results confirmed that with a cut-off point of >65 [13-26], the LIAISON® MeMed BV® test had a Se of 79.2% and an Sp of 91.2%. Increasing the cut-off to > 90 points resulted in a reduced Se (57%) but improved Sp (95.9%). Applying the Youden index, a CP of >50 points achieved a Se of 84.1% and a Sp of 88.2%. These findings highlight the importance of continued research to validate CPs across different subgroups. Compared to the LIAISON® MeMed BV®, PCT showed lower diagnostic accuracy in this study, with CPs ≥0.25 ng/ml and ≥0.50 ng/ml performing less effectively despite these CPs being identified in literature as the most suitable for predicting BI diagnosis [10], and predicting bacteremia [9], respectively. Importantly, our study is the first to report the LIAISON® MeMed BV® test accuracy in the true bacteremia (AUC-ROC: 0.936), which requires further validation in future studies

Oved et al. [13] reported similar findings, with an AUC of 0.94 (95% CI: 0.92–0.96) and superior performance compared to PCT, CRP and leukocyte count. Ashkenazi-Hoffnung et al. [22] reported similar results in adult patients (AUC > 0.92), with a sensitivity of 92.6% and specificity of 95.7% and estimated reduction in unnecessary antibiotic use by 88% [22]. The reported accuracy was superior to PCT and CRP. Similarly, Stein et al. [21] and Halabi et al. [23] demonstrated high diagnostic accuracy as well, with a sensitivity and specificity of 93% /91%and 98.1% / 88.4%, respectively. Most recently, Bachur et al. [27] further validated the test in a multicenter study and achieved a sensitivity of 90%, specificity of 92.8%, and an NPV of 98.8%. Important, all previously published studies have described results in patients with suspected acute infection but, to our knowledge, our study is the first to report data on a subgroup of patients aged ≥65 years and those with con-

firmed bacteremia. Despite these strengths, our study has limitations. The single-center design and convenience sampling introduced the possibility of selection bias. The sample size (258 patients) was limited and heterogenous, including a variety of infection types (e.g., LRTI, UTI, abdominal infections, fever of unknown origin) and diverse bacterial and viral pathogens. Additionally, the differential characteristics between these subgroups were not analyzed.

Despite these limitations, the study reflects the clinical reality of our ED and local patient population. Even with recent advancements in infectious diseases diagnostics, timely identification of bacterial infections remains a challenge, complicating appropriate administration of early antibiotics in the ED. Future prospective, multicenter studies with power-calculation informed sample sizes are needed to validate or refine these findings.

Future studies must evaluate the LIAISON® MeMed BV® test alongside other IRIBs to assess its diagnostic and prognostic accuracy for BI, but also for bacteremia and patient outcomes such as severity, ICU admission, and mortality [31-35]., The ultimate goal would be to identify the IRIB or combination thereof that is most effective for supporting routine clinical practice in the ED [12,32,33].

In conclusion, this study suggests that the LIAISON® MeMed BV® test is a promising tool for diagnosing bacterial infections in adult patients treated in the ED with clinical suspicion of an acute infection. It achieved better diagnostic accuracy than PCT, CRP and leukocyte count.

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CONFLICT OF INTERESTS

The authors declare no conflicts of interest regarding this article. AJJ has participated in scientific meetings organised by Roche, Thermo Scientific Biomarkers, B.R.A.H.M.S. AG, ViroGates & Biomerieux. No author received financial compensation for participating in this work.

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