Serial Measurement of Pancreatic Stone Protein for the Early Detection of Sepsis in Intensive Care Unit Patients: A Prospective Multicentric Study

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Abstract

Background

The early recognition and management of sepsis improves outcomes. Biomarkers may help in identifying earlier sub-clinical signs of sepsis. We explored the potential of serial measurements of C-reactive protein (CRP), procalcitonin (PCT) and pancreatic stone protein (PSP) for the early recognition of sepsis in patients hospitalized in the intensive care unit (ICU).

Methods

This was a multicentric international prospective observational clinical study conducted in 14 ICUs in France, Switzerland, Italy, and the United Kingdom. Adult ICU patients at risk of nosocomial sepsis were included. A biomarker-blinded adjudication committee identified sepsis events and the days on which they began. The associations of clinical sepsis diagnoses with the trajectories of PSP, CRP, and PCT in the 3 days preceding these diagnoses of sepsis were tested for markers of early sepsis detection. The performance of the biomarkers in sepsis diagnosis was assessed by receiver operating characteristic (ROC) analysis.

Results

Of the 243 patients included, 53 developed nosocomial sepsis after a median of 6 days (interquartile range, 3–8 days). The association of clinical sepsis diagnosis with an increase in a biomarker value in the 3 days preceding this diagnosis was stronger for PSP ($p = 0.003$) than for PCT ($p = 0.025$) and CRP ($p = 0.009$). The area under the ROC curve at the time of clinical sepsis was similar for all markers (PSP, 0.75; CRP, 0.77; PCT, 0.75).

Conclusions

While the diagnostic accuracy for sepsis of PSP, CRP and PCT were similar in this cohort, serial PSP measurement demonstrated an increase of this marker the days preceding the onset of signs necessary for a clinical diagnosis the sepsis. This observation justifies further evaluation of the potential clinical benefit of serial PSP measurement in the management of critically ill patients developing nosocomial sepsis.

Trial registration

The study has been registered at ClinicalTrials.gov (no. NCT03474809), on March 16, 2018.

https://www.clinicaltrials.gov/ct2/show/NCT03474809?term=NCT03474809&draw=2&rank=1

Background
Sepsis, if not recognized and managed early, may evolve rapidly into life-threatening septic shock and multiple organ failure (1–3). Sepsis and septic shock remain challenging global health problems associated with persistently high morbidity and mortality; in 2017, an estimated 48.9 million cases of sepsis were recorded worldwide, with 11.0 million related deaths, representing one-fifth of all causes of death (4). Accordingly, guidelines systematically emphasize the early recognition and aggressive management of sepsis, with combined early antibiotic treatment and support to prevent organ dysfunction (1, 5, 6). Currently, the confirmation of sepsis diagnosis is based largely on nonspecific clinical signs, laboratory findings and medical scores, which are usually obtained after sepsis onset. Despite extensive study, no biomarker with the capacity to detect sepsis quickly enough and with a high degree of diagnostic accuracy has been identified (7). C-reactive protein (CRP) is a well characterized inflammatory marker widely used to help in the diagnosis of infection. Procalcitonin (PCT) has been extensively evaluated in the last 20 years as a marker of bacteremia. Even if CRP and PCT are commonly used in the context of the diagnosis of sepsis, both have shown suboptimal performance (8).

Pancreatic stone protein (PSP) is a C-type lectin protein that triggers polymorphonuclear cell activation and has shown proinflammatory activity in vitro (9). In an unselected cohort of critically ill adults, PSP was found to be superior to PCT and other sepsis biomarkers for the accurate identification of sepsis (10). An increase in PSP level preceding the development of sepsis has recently been demonstrated in a cohort of severely burnt patient (11). The diagnostic performance of PSP, alone and in combination with other markers or clinical scores, has been evaluated further in several studies conducted in adults, children, and neonates, in both, intensive care units (ICUs) and emergency departments (12). In contrast to PCT and CRP, PSP was found to be a prognostic marker for ICU mortality (13–15). In addition, PSP can be measured with ‘point-of-care’ device within 5 minutes using a single drop of whole blood (16), leading the way for simple, on-demand, around-the-clock, serial biomarker assessments instead of one-off measurements upon the clinical suspicion of sepsis.

We hypothesized that timely identification of changes in biomarker levels may help identify sepsis before the onset of clinical signs. We therefore designed a multicentric international prospective blind observational study to explore the ability of serial PSP measurements to identify nosocomial sepsis before the onset of clinical signs required to clinically diagnose sepsis in an adult ICU population, and compared it with CRP and PCT.

**Study Design And Methods**

**Study design**

This multicentric biomarker-blinded prospective observational clinical study was conducted in 14 ICUs in France, Switzerland, Italy, and the United Kingdom, see Additional Table 1. Approval was obtained from the ethics committees of all participating sites. The study has been registered at ClinicalTrials.gov (no. NCT03474809).

**Patient population**
All patients older than 18 years admitted to the ICU and with an expected ICU stay of at least 7 days and/or expected to be mechanically ventilated for at least 5 consecutive days were screened for study inclusion (Additional Table 2). Patients with a clinical diagnosis of sepsis or suspicion of sepsis at the admission were not included. Written informed consent to participation and any study-related assessment was obtained from all patients before their inclusion in the study. Written informed consent was obtained according to the specific requirements of each center's ethics committee.

At least 40 patients who developed sepsis after study enrolment were planned to be included. Based on recently published data (17–19), the expected incidence of sepsis in the targeted ICU population was estimated conservatively to be 15%. This value corresponded to a sample of 267 patients, to which we added 10% to compensate for withdrawal and loss to follow-up.

**Trial procedure and definitions**

Patients were managed according to the centers' standard clinical practices, including those for the diagnosis, assessment, and treatment of sepsis. Blood samples were collected daily for biomarker (PCT, CRP, and PSP) measurements. Patients were followed until death or discharge from the ICU or for 30 days, whichever occurred first. The Sepsis-3 criteria were used to define sepsis (1), and microbiological procedures were performed to diagnose infections responsible for sepsis according to local protocol.

**Measurement of biomarkers**

Daily PSP levels were determined at the end of the study period with the CE-marked IVD PSP capsule on the point-of-care abioSCOPE® device (Abionic SA; Additional Figure 1). CRP and PCT measurements were performed by a central laboratory using a Tina-quant® C-Reactive Protein Gen.3 (Roche Diagnostics) and a Liaison® Brahms PCT® for PCT (DiaSorin), respectively. All instruments were used according to the manufacturers' instructions.

**External adjudication committee**

An independent endpoint adjudication committee (EAC) composed of three ICU experts was formed. Two non-chair EAC members retrospectively and independently reviewed case report forms for each patient and determined whether a septic event had occurred during the patient's ICU stay (including on the day of inclusion), and the day on which the event had started. Discordant determinations were arbitrated by the EAC chair. The EAC had access to all case report forms, including results of all microbiological investigations, CRP and PCT measurements taken in the ICUs as part of standard care, but was blinded to centrally measured PSP, PCT, and CRP levels and the investigators' diagnoses of sepsis.

**Patient-related data**

Data collected at the time of inclusion were: demographic characteristics, reason for ICU admission, medical history, and Charlson comorbidity index. Additional clinical data were collected on day 1 and daily thereafter when measurements were performed as part of standard care; these data included vital
signs (temperature, heart rate, and blood pressure), Sequential Organ Failure Assessment (SOFA) scores, \( \text{PaO}_2/\text{FiO}_2 \) ratios, hematological data, clinical chemistry parameters, need for organ support (ventilation and use of vasoactive drugs) and microbiological data. In addition to the collection of data on antibiotic treatments (drug name, dose, schedule, route, and indication), meticulous assessments for sepsis detection were carried out daily until ICU discharge, death, withdrawal, or day 30, whichever came first.

**Statistical analyses**

Discrete values are described as counts (percentages) and continuous variables are described as means with standard errors or medians with interquartile ranges (IQRs), as appropriate. The missing biomarker values were imputed by carrying the last observation forward, and multiple consecutive missing values were reported as missing. Based on EAC decisions, the patients were allocated to sepsis (septic event occurrence during the study period) and no-sepsis (no septic event during the study period) groups. In the sepsis group, the event days were set as the days on which the first septic events began, according to the EAC. In the no-sepsis group, the event days were set to day 7 of patients' ICU stays, when more than 50% of adjudicated septic events occurred, or the days of discharge for patients with ICU stays of fewer than 7 days. Biomarkers average trajectories were visualized accordingly. All statistical analyses were performed using R version 4.0.2.

**Biomarkers dynamics and progression toward sepsis**

To explore the dynamics of serial biomarker measurement throughout the study period, we modeled biomarker courses in the 3 days prior to EAC sepsis diagnoses by fitting a linear mixed-effect model with PSP, CRP, and PCT as response and following explanatory variables: patient-specific random effect, group, day-to-event and group by day-to-event interaction as fixed-effects (estimates are provided in Additional Table 3). According to Van Breukelen (20) “testing absence of group by time interaction is equivalent to testing the hypothesis of no group effect on the change” in a response variable over days.

**Assessment of biomarker accuracy in diagnosing sepsis**

The joint performance of the biomarkers in the diagnosis of sepsis on the day it occurred as per EAC decision was assessed using receiving operating characteristic (ROC) analysis. To account for differences among study sites and incidences of nosocomial sepsis, a linear mixed-effects logistic regression model was used with the center serving as a random intercept and biomarkers serving as fixed events (estimates are provided in Additional Table 4) (21).

**Results**

**Baseline characteristics of the study population**

From June 2018 to March 2019, 297 patients were enrolled in this study. Fifty-four of these patients were excluded from the analysis due to the presence of infection and/or sepsis at the time of inclusion as
adjudicated by the EAC \((n = 33)\), ICU stays < 48 hours \((n = 15)\), withdrawal \((n = 5)\), and screening failure \((n = 1)\) (Figure 1). The characteristics of the remaining 243 patients are summarized in Table 1. The cohort contained 153 (63%) men and had a median age of 65 years and a median SOFA score of 6 at the time of admission. The most common comorbidities were cancer (16%) and heart (15%), pulmonary (13%), renal (12%), and hepatic (7%) disease. Vasopressors were administered to 39% of patients, and 77% of patients required mechanical ventilation. The main reasons for ICU admission were acute central nervous system disease (39%), cardiovascular disease (31%), and abdominal/digestive conditions (19%; Table 1). The median ICU length of stay of the entire cohort was 9 days (IQR: 6 to 17) and 7 days (IQR: 5 to 13 days) for the "no-sepsis" patients and 21 days for patients who developed sepsis (IQR: 14 to 27 days). ICU mortality rate in the study cohort was 16%. The baseline clinical characteristics of patients who did and did not develop sepsis during the study period were similar.

According to the EAC decisions, 21.8\% \((n = 53)\) of the patients developed sepsis and 78.2\% \((n = 190)\) did not. The EAC chair arbitrated disagreements about sepsis presence/absence and day of initiation in 31\% of cases. The median interval from study inclusion to sepsis development was 6 days (IQR, 3–8 days). The characteristics of patients who developed sepsis are provided in Table 2. Sepsis was attributed most frequently to respiratory tract infections (62\%), followed by bloodstream infections (11\%) and urinary tract (9\%) infections.

**Time courses of biomarkers for sepsis prediction**

The time courses of biomarkers until sepsis (“sepsis” group), and until day 7 or discharge for ICU stays of fewer than 7 days (“no-sepsis” group) are shown in Figure 2. All biomarker values increased for several days before the clinical diagnosis of sepsis (PSP, 5 days; PCT, 3 days; CRP, 2 days). The association of a clinical sepsis diagnosis with a biomarker increase over the 3 days preceding this diagnosis was stronger for PSP \( (p = 0.003) \) than for PCT \( (p = 0.025) \) and CRP \( (p = 0.009) \).

**Accuracy of individual biomarkers and their combination in sepsis diagnosis**

Areas under receiver operating characteristic curves (AUROCCs) on the day of sepsis diagnosis according to the blinded EAC were similar for all three biomarkers \{PSP, 0.75 [95\% confidence interval (CI) 0.67–0.82]; CRP, 0.77 [95\% CI 0.69–0.84] PCT, 0.75 [95\% CI 0.68–0.83]; Table 3\}. The combined use of PSP with CRP improved the accuracy to 0.79 (95\% CI 0.72–0.86). The addition of PCT to this combination did not further improve the accuracy or sensitivity, and only marginally improved the specificity.

**Discussion**

This prospective multicentric study evaluated the potential of serial host protein biomarkers measurement, in particular the relatively new marker PSP, for the early identification of nosocomial sepsis in ICU patients. In the study cohort of critically ill patients at high risk of complications, in which one in five developed sepsis, the baseline clinical characteristics, including severity scores and the need for mechanical ventilation and vasopressor support, were similar among patients who did and did not
develop sepsis. The main novel finding of this study is the significant association of the clinical diagnosis of sepsis with the continuous increase in the PSP level in the 3 days before this diagnosis. This association corroborates recent observations made in a cohort of patients with severe burns, in which PSP levels increased constantly in the days preceding sepsis and this increase was greater in patients with septic shock (11, 22).

In addition, this study confirmed that the accuracy of clinical sepsis diagnosis based on PSP values was similar to that of diagnoses based on PCT and CRP values. In an unselected population of critically ill patients, the use of PSP values to distinguish sepsis from non-infectious systemic inflammatory response syndrome (SIRS) at the time of ICU or high-dependency care admission was more accurate than was the use of PCT values (10). Furthermore, a recent meta-analysis of data from 631 ICU patients, of whom 371 had infections or sepsis, confirmed that these conditions could be identified accurately based on PSP values [AUROCC = 0.81, slightly superior to those for PCT (0.78) and CRP (0.77)]. The combined use of PSP and CRP values increased this accuracy (AUROCC = 0.90) (Prazak J. et al., e-ISICEM, Sept. 15-18.2020), similarly to what was observed in this study where the combination of CRP and PSP increased the accuracy to 0.79, although the overlaps of the 95% confidence intervals preclude to draw a robust statement regarding the significance of this increase.

This study has several strengths. First, it is the first international multicentric prospective study in which a host protein blood biomarker, the PSP, was measured daily in an ICU setting for the early detection of nosocomial sepsis using a point-of-care device offering on-demand test results in less than 10 minutes. Second, nosocomial sepsis was diagnosed by an independent adjudication committee composed of intensivists blinded to biomarker results. Third, this study determined the accuracy of single and combined biomarkers in the diagnosis of nosocomial sepsis in critically ill patients. However, several limitations of this study must be considered. Given its multicentric international design, the recruitment rate and sepsis incidence differed among study sites, in association with differences in preventive measures against nosocomial infection and sepsis development. In addition, although the expected number of patients who developed sepsis was reached, the low absolute number of sepsis events precluded subgroup analysis by site or country. Finally, this study was conducted with a subgroup of ICU patients who were expected to have prolonged ICU stays but were admitted free of infection, which precludes the extension of our observations to other settings.

In the absence of an unambiguous definition of sepsis and highly accurate diagnostic tools the presence/absence of sepsis at any given days of an ICU stay was adjudicated by an expert committee. Discordant results using such approach have already been reported and vary considerably within sepsis diagnosis subgroups and clinical question (23)(24). In our study not only the presence or absence of sepsis was adjudicated but also the day of event: this additional parameter contributed to the rate of discordance observed, reflecting the diagnostic challenges that clinicians are facing for the timely diagnosis of sepsis.
The inclusion in such diagnostic strategies of a risk-stratification of patients, for example based on clinical score such as the SOFA and the Acute Physiology And Chronic Health Evaluation (APACHE) scores, or of algorithms offering pretest probability, would allow to define economically viable and clinically meaningful strategies to closely monitor patients who will benefit the most of such approach. In respect to that, the kinetic of biomarkers in response to a sepsis event should be further evaluated to determine the optimal dosage frequency of biomarkers associated with the best clinical benefit.

The clinical significance of an increase in the PSP level the days preceding the clinical diagnosis of sepsis may prompt changes in the management of patients at risk of nosocomial sepsis by triggering early diagnostic procedures and the timely establishment of appropriate treatment, for example to identify the source of the infection and the pathogen, and to assess the clinical utility of preemptive antibiotic therapy. The results of this study certainly serve as a robust early basis for future validation studies of such innovative approach, including studies conducted in wards outside of the ICU to determine how serial PSP measurement could enable the early detection of sepsis before the onset of clinically overt symptoms in patients at risk.

**Conclusions**

The diagnostic accuracy of PSP, CRP and PCT for the diagnosis of sepsis at the time the EAC identified it were similar. Serial measurements of biomarker revealed that blood PSP levels increased incrementally 3 days before the clinical diagnosis of nosocomial sepsis in critically ill patients, allowing the early detection of sepsis before the appearance of signs and symptoms. This association was stronger than those for PCT and CRP levels. These results justify further evaluation of the potential of serial PSP measurement in the diagnosis, management and clinical outcome of critically ill patients developing nosocomial sepsis.

**Abbreviations**

APACHE; Acute physiology and chronic health evaluation

AUROCC; Areas under receiver operating characteristic curves

CI; confidence interval

CRP; C-reactive protein

EAC; External adjudication committee

ICU; Intensive care unit

IQR; Interquartile range

IVD; In vitro diagnostic
Declarations

Ethics approval and consent to participate

Approval was obtained from the ethics committees of all participating sites. The study has been registered at ClinicalTrials.gov (no. NCT03474809). Written informed consent to participation and any study-related assessment was obtained from all patients before their inclusion in the study. Written informed consent was obtained according to the specific requirements of each center's ethics committee.

Consent for publication

N/A. The data presented are anonymized, so consent for publication is not required

Availability of data and materials

All data generated or analyzed during this study are included in this published article and its additional files.

Competing interests

Irina Irincheeva is affiliated with CTU Bern, University of Bern, which has a staff policy of not accepting honoraria or consultancy fees. However, CTU Bern is involved in design, conduct, or analysis of clinical studies funded by not-for-profit and for-profit organizations. In particular, pharmaceutical and medical device companies provide direct funding to some of these studies. For an up-to-date list of CTU Bern's conflicts of interest see http://www.ctu.unibe.ch/research/declaration_of_interest/index_eng.html. Pierre-François Dequin declares that his institution (Centre Hospitalier Régional Universitaire de Tours, Tours, France) received grants for the inclusion of patients in the study. Bruno François declares receiving consultancy fees from Abionic. The other authors declare that they have no conflicts of interest.

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proprietary nanofluidic technology to measure pancreatic stone protein. Fabien Rebeaud was involved in study design and writing of the manuscript.

**Authors' contributions**

JP, PE and BF were involved in the conception and the design of the study. II performed the statistical analyses. JP, PE, BF, FR, II and TD analyzed the data and wrote the manuscript. JP, TD, JLP, DM, AG, PFD, CG, YAQ, GZ, DB, AL, BCB, DW, DS, II, LG, FR, IM, PE, BF have read and accepted the entire content of this submitted manuscript, and approved submission.

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Tables

Table 1. Clinical characteristics of patients at the time of study admission (day 1 of intensive care unit stay) for the entire cohort and for the two sub-groups “sepsis” and “no-sepsis”.
Table 2. Characteristics of patients in the sepsis group at the time of endpoint adjudication committee diagnosis of sepsis

| Clinical Characteristics                  | Total     | No-Sepsis | Sepsis    |
|------------------------------------------|-----------|-----------|-----------|
| Number of patients (n, %)                | 243 (100%)| 190 (78.2%)| 53 (21.8%)|
| Gender (n, %)                            |           |           |           |
| Male                                     | 153 (63%) | 113 (59%) | 40 (75%)  |
| Female                                   | 90 (37%)  | 77 (41%)  | 13 (25%)  |
| Age, median [IQR]                        | 65 [54, 72.5]| 65 [54, 72]| 64 [55, 73]|
| SOFA score, median [IQR]                 | 6 [5, 9]  | 6 [4.9]   | 7 [5, 9]  |
| Charlson score (n, %)                    |           |           |           |
| Charlson score 0                         | 51 (21%)  | 46 (24%)  | 5 (9%)    |
| Charlson score 1-2                       | 84 (35%)  | 60 (32%)  | 24 (45%)  |
| Charlson score 3-4                       | 47 (19%)  | 34 (18%)  | 13 (25%)  |
| Charlson score 5 and more                | 52 (21%)  | 42 (22%)  | 10 (19%)  |
| Non-reported Charlson score              | 9 (4%)    | 8 (4%)    | 1 (2%)    |
| Reason for ICU admission (n, %)          |           |           |           |
| CNS (trauma, stroke, haemorrhage)        | 94 (39%)  | 74 (39%)  | 20 (38%)  |
| Cardiovascular                           | 76 (31%)  | 60 (32%)  | 16 (30%)  |
| Abdominal/digestive                      | 45 (19%)  | 32 (17%)  | 13 (25%)  |
| Respiratory                              | 18 (7%)   | 16 (8%)   | 2 (4%)    |
| Metabolic                                | 9 (4%)    | 7 (4%)    | 2 (4%)    |
| ICU treatments (n, %)                    |           |           |           |
| Mechanical ventilation                   | 187 (77%) | 143 (75%) | 44 (83%)  |
| Vasopressors                             | 95 (39%)  | 69 (36%)  | 26 (49%)  |
| No-reported Vasopressors                 | 16 (7%)   | 15 (8%)   | 1 (2%)    |
| Comorbidities (n, %)                     |           |           |           |
| Cancer                                   | 40 (16%)  | 33 (17%)  | 7 (13%)   |
| Heart disease                            | 35 (15%)  | 26 (14%)  | 9 (17%)   |
| Pulmonary disease                        | 31 (13%)  | 26 (14%)  | 5 (10%)   |
| Renal disease                            | 29 (12%)  | 23 (12%)  | 6 (12%)   |
| Liver disease                            | 17 (7%)   | 12 (6%)   | 5 (9%)    |
| ICU length of stay, median [IQR]         | 9 [6, 17] | 7 [5, 13] | 21 [14, 27]

ICU, intensive care unit; IQR, interquartile range; SOFA, sequential organ failure assessment; CNS, central nervous system.

Table 2. Characteristics of patients in the sepsis group at the time of endpoint adjudication committee diagnosis of sepsis
Values are shown with 95% confidence intervals. Data are from 233 patients (sepsis, \(n = 53\); no sepsis, \(n = 180\)).

PSP, pancreatic stone protein; CRP, C-reactive protein; PCT, procalcitonin; IQR, interquartile range; ICU, intensive care unit; SOFA, sequential organ failure assessment.

**Table 3. Center-adjusted receiver operating characteristic results reflecting the ability of pancreatic stone protein, C-reactive protein, procalcitonin, and their combinations to discriminate the presence and absence of sepsis.**

| Parameter              | Accuracy   | Sensitivity   | Specificity   | LR−       | LR+       |
|------------------------|------------|---------------|---------------|-----------|-----------|
| PSP                    | 0.75 (0.67,0.82) | 0.74 (0.62,0.86) | 0.67 (0.60,0.74) | 0.40 (0.25,0.63) | 2.21 (1.70,2.87) |
| CRP                    | 0.77 (0.69,0.84) | 0.66 (0.55,0.81) | 0.77 (0.71,0.83) | 0.42 (0.28,0.62) | 2.91 (2.11,4.02) |
| PCT                    | 0.75 (0.68,0.82) | 0.72 (0.60,0.84) | 0.69 (0.62,0.76) | 0.41 (0.27,0.64) | 2.31 (1.75,3.04) |
| PSP-CRP                | 0.79 (0.72,0.86) | 0.72 (0.60,0.84) | 0.73 (0.67,0.80) | 0.39 (0.25,0.60) | 2.69 (2.00,3.61) |
| PSP-PCT                | 0.75 (0.68,0.83) | 0.76 (0.64,0.87) | 0.65 (0.58,0.72) | 0.38 (0.23,0.61) | 2.16 (1.68,2.77) |
| CRP-PCT                | 0.77 (0.70,0.84) | 0.68 (0.55,0.81) | 0.77 (0.71,0.83) | 0.42 (0.28,0.62) | 2.91 (2.11,4.02) |
| CRP-PCT-PSP            | 0.79 (0.72,0.86) | 0.72 (0.60,0.84) | 0.74 (0.68,0.81) | 0.38 (0.25,0.59) | 2.81 (2.08,3.79) |

PSP, pancreatic stone protein; CRP, C-reactive protein; PCT, procalcitonin; LR−, likelihood ratio.
Figure 1
Flow of patient enrollment. ICU, intensive care unit; EAC, endpoint adjudication committee.

Supplementary Files
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- AdditionalFigure1.eps