Research Article

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# Evaluation of qSOFA and variation of hematochemical profile in cats naturally infected with feline panleukopenia virus

https://doi.org/10.1515/ovs-2022-0118
received November 22, 2022; accepted February 20, 2023

**Abstract:** Feline panleukopenia (FP) is a fatal viral disease that predisposes cats to sepsis and organ failure. Owing to a wide variety of clinical findings, hematochemical examinations are significant for the determination of early signs of disease-related complications. The aim of this study is to investigate the diagnostic efficacy of certain hematochemical parameters together with quick Sepsis-related Organ Failure Assessment (qSOFA) in cats with FP. A total of 10 healthy and 30 panleukopenic cats were included in this study. Physical examinations revealed that the body temperature was highest in septic panleukopenic cats ($p < 0.009$) and they had higher qSOFA scores ($p = 0.000$). Hemogram analysis revealed that leukocyte, lymphocyte, granulocyte, erythrocyte, and hemoglobin levels were lower in non-septic panleukopenic cats compared with the healthy ones ($p < 0.030$). Also, monocyte and mean corpuscular hemoglobin levels were lower in septic ones ($p < 0.048$). Serum biochemistry profiling revealed higher blood urea nitrogen, creatinine, alanine aminotransferase, lactate dehydrogenase, total bilirubin, and C-reactive protein levels in panleukopenic cats ($p < 0.033$). As a result, it was concluded that although the qSOFA is not sufficient to distinguish sepsis in cats, unlike dogs, in order to achieve a positive clinical outcome, when evaluated together with hematochemical variables, it may help in making early diagnosis of FP-related complications.

**Keywords:** cat, feline panleukopenia, diagnosis

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## 1 Introduction

Feline panleukopenia (FP) is the oldest known viral disease of cats and has been protected by vaccination since 1934 with formalin-inactivated tissue extracts from infected cats [1]. Although the incidence of the disease has decreased with vaccination rates of up to 82% in 2016, sporadic outbreaks still occur in some countries, including the United Kingdom, Australia, and the United States of America [1,2].

FP infection often occurs in unvaccinated and/or incompletely vaccinated cats [3]. The main route of transmission of the feline parvovirus (FPV), which is shed in high amounts in saliva, urine, feces, and vomitus, is the orofecal route and, more rarely, inhalation of aerosolized virus [4]. Since the virus only replicates in actively diving S-phase cells, it has tropism to lymphoid tissue, bone marrow, intestinal crypt epithelium, and to Purkinje cells of the cerebellum in neonatals younger than 10 days old [5]. In addition to peracute death due to septic shock in cats younger than 2 months of age, the most common clinical presentation of FP is fever up to 41°C, lethargy, anorexia, vomiting, diarrhea, and severe dehydration [6]. Also, hypersalivation due to nausea and thickened intestinal loops and enlarged mesenteric lymph nodes can be detected on abdominal palpation [2]. Hemorrhagic diarrhea is very rare in cats compared to parvovirus infection of dogs [7]. Common laboratory findings in FP-affected cats are leukopenia (65–75% of cases), thrombocytopenia (55% of cases) [6], hypoalbuminemia (45–52% of cases), hypoproteinemia (30% of cases), and elevated liver enzyme levels (27% of cases) [8]. As reported previously, the diversity and variable incidences of clinical and laboratory findings may complicate the early diagnosis of the disease. In addition, the increased risk of circulatory shock, organ dysfunction, sepsis, and disseminated intravascular coagulopathy (DIC) in cats with FPV makes clinical diagnosis more difficult because the clinical manifestation of septic cats is different from that of septic dogs.

This difference also increases the importance of early diagnosis [9]. Fecal antigen enzyme-linked immunosorbent assay (ELISA) test kits developed and frequently used for diagnostic purposes may cause false positive results after vaccination with modified live vaccine (MLV) for at least 14 days [10]. Also, commercial polymerase chain reaction (PCR) assays may not be able to distinguish between feline and canine parvovirus strains. Moreover, diagnostic methods such as virus isolation, hemagglutination assays, and immunoelectron microscopy are time-consuming and require equipment and expertise [2,11]. For this reason, when routine laboratory analyses including hemogram and serum biochemistry variables are evaluated together with clinical scores such as quick Sepsis-related Organ Failure Assessment (qSOFA), which is frequently evaluated in septic dogs [12], it can facilitate the diagnosis of complications such as disease-related organ failure and predict mortality and length of stay in the intensive care unit (ICU) in the clinical setting.

FP is diagnosed on the basis of history, clinical, and hematochemical findings, and by virus detection using commercial fecal ELISA kits [2]. Even though they may seem deceivingly basic, routine clinical and laboratory examinations allow determination of early signs of disease and severe conditions. Thus, they have an important role in clinical practice in both diagnosis and management. Also, studies conducted under experimental conditions might not represent the findings in naturally infected cats. Therefore, the aim of this study is to investigate the diagnostic efficacy of the qSOFA score, which has been less studied in cats as opposed to dogs, along with the physical and laboratory examinations including hemogram and serum biochemistry profile in cats naturally infected with FPV with and/or without sepsis.

# 2 Materials and methods

The study was designed to include the cats presented to the Animal Hospital of Veterinary Faculty, Harran University, Turkey, between 2021 and 2022 that were screened for FPV infection as part of the medical workup.

## 2.1 Animals

The Panleukopenia group of the present study consisted of 30 client-owned unvaccinated cats aged between 1 and 11 months, which were admitted for diagnosis and treatment purposes with clinical findings compatible with FP such as diarrhea, vomiting, inappetence, weight loss, dehydration, and bone marrow suppression (secondary bacterial infections). The Control group consisted of ten cats of similar age and body weight, which were determined to be healthy by clinical and laboratory examinations. The median body weight of the panleukopenic cats was 1.4 (0.8–2.2) and the healthy cats were 1.55 (1–2) kg ($p < 0.648$). While 14 of the panleukopenic cats were male and 16 were female, 5 of the healthy cats were male and 5 were female.

**Ethical approval:** The research related to animal use has been complied with all the relevant national regulations and institutional policies for the care and use of animals. We informed and received the permission of the owners of the cats included in this study to take samples used in the present study. Samples were collected as per standard sample collection procedure without any harm to animals.

## 2.2 Physical examinations

Physical examinations, including lung and heart auscultation, evaluation of mucous membrane, capillary refill time (CRT), palpable lymph nodes, mental state, and systolic blood pressure (SBP), were performed by the same personnel with the same examination protocol. Feline ataxia was not present in any of the cats with suspected panleukopenia in the present study. Thus, it was ensured that the diseased cats in the present study were exposed to the virus naturally via the orofecal route, not *in utero*. During SBP measurement, to minimize stress, cats were allowed to assume a comfortable position with only gentle restraint by their owners and remained in the same position throughout the measurement. An inflatable cuff was applied to one of the legs of the cats and the cuff was temporarily filled with air until the blood flow was impeded. Cats that needed very strict restrain or were very aggressive were excluded from the study. Five to seven consecutive and consistent measurements were made, all readings were recorded whether or not used to calculate SBP, and the SBP was calculated as the mean of these using a multi-parameter veterinary monitor (BM7Vet Elite, Bionet, USA).

## 2.3 Sepsis criteria and detection of its presence

The criteria for the presence of sepsis in the panleukopenic cats were as follows: (1) body temperature: >39.7 or

<37.7°C, (2) heart rate: >225 or <140 bpm, (3) respiratory rate: >40 bpm, and (4) total WBC count: >19,500 cells or <5,000 cells [13]. Since the classical or hyperdynamic phase, which is frequently observed in septic dogs, is rarely observed in cats and, unlike dogs, clinical findings, such as pale mucous membranes, prolonged CRT, and weak or absent pulse, are evident in cats [14], these parameters were also considered in addition to the sepsis criteria.

## 2.4 qSOFA criteria and calculation of scores

Since the Sepsis-3 consensus suggested including the presence of an organ failure in the presence of sepsis, three criteria for qSOFA were considered in this study [15]. They are as follows: (1) altered mental state (0 = normal; 1 = able to stand unaided, alert but stagnant; 2 = able to stand with assistance, environmentally sensitive but stagnant; 3 = unable to stand, alert; 4 = unable to stand, apathetic), (2) respiratory rate >22 breaths/min, and (3) SBP < 100 mmHg. It was reported that the qSOFA score >2 is associated with higher mortality and longer ICU duration [16]. Septic cats included in the study were evaluated based on respiratory rate >22 breaths/min, SBP <100 mmHg, or presence of altered mental status in terms of qSOFA evaluation. The qSOFA score was accepted as 1 for each criterion.

## 2.5 Application of rapid diagnostic test kits

Fecal samples were obtained from FP suspected cats with anal or rectal swabs. At first, swabs were wetted with sterile isotonic and the sample was taken rectally in cases with no feces in the anus and perineum. Due to its low-to-moderate sensitivity (50–80%) and good-to-excellent specificity (94.2–100%), the IDEXX SNAP Parvo test was used for diagnosis [8,17] and the tests were performed by trained research assistants at the central laboratory according to the manufacturer's instructions. Positive results were recorded as weakly positive or positive according to color intensity.

## 2.6 Inclusion criteria

Inclusion criteria to suspect FP were the presence of clinically compatible findings (absence of diarrhea, vomiting, lethargy, and fever in kittens; presence of anorexia, hyporexia, lethargy, vomiting, and diarrhea in older cats) and abnormal laboratory findings (leukopenia and anemia) along with positive fecal IDEXX SNAP Parvo test result [18]. Cats with a previous history of disease or had blood transfusion were not included in the study. All cats included in the study were examined for feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV) presence (IDEXX SNAP FIV/FeLV Combo Test; IDEXX Laboratories) using rapid diagnostic test kits measuring p27 antigen for FeLV (sensitivity of 98.6% and specificity of 98.2%) and antibodies for FIV (sensitivity of 93.5% and specificity of 100%). All cats were tested once and cats with insufficient/suspicious results were excluded from the study. In addition, microscopic fecal examinations of all the cats were performed and no parasites and/or eggs were found.

## 2.7 Blood sampling and performing hemogram and biochemical analyses

Venous blood samples were obtained from all the cats with minimal restraint and patient stress by vena cephalica or vena jugularis venepuncture (3–5 mL). Hematological parameters (leukocyte [WBC], lymphocyte, monocyte, granulocyte, erythrocyte [RBC], mean corpuscular volume [MCV], hematocrit [Hct], mean corpuscular hemoglobin [MCH], mean corpuscular hemoglobin concentration [MCHC] and hemoglobin [Hb]) were measured from blood samples with $K_3$EDTA using an automated hematology analyzer (Sysmex poch-100i, Canada) within 5–10 min after sampling. Serum biochemistry parameters (blood urea nitrogen [BUN], creatinine, aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP], lactate dehydrogenase [LDH], phosphorous, cholesterol, total bilirubin, albumin, total protein, and C-reactive protein [CRP]) were measured from serum samples (after centrifugation of serum tubes at 5,000 rpm for 10 min) using automatic biochemistry analyzer (Spotchem EZ SP-4430, Arkray, Japan) within 10–20 min after sampling. All results were compared with laboratory reference values.

## 2.8 Statistical analysis

Data analysis was evaluated using SPSS 25.00 (SPSS for Windows) statistical software and one sample Kolmogorov–Smirnov test was applied to determine whether all data were parametric or non-parametric. Non-parametric data

were evaluated as median (min, max) using Mann–Whitney U, Kruskal–Wallis test. Data analysis of three groups was performed with one-way ANOVA or Kruskal–Wallis test depending on the distribution pattern. In addition, in order to measure the statistical relationship, or association, between qSOFA score and the hematochemical profile variables Spearman's rank correlation coefficient test was performed. The strength of the correlation was interpreted using the following guide for the absolute value of rs: 0.00–0.19 as very weak, 0.20–0.39 as weak, 0.40–0.59 as moderate, 0.60–0.79 as strong, and 0.80–1.0 as very strong. In order to investigate how accurately the present diagnostic tests discriminate the presence of sepsis and to determine optimal cut-off values receiver operating characteristic (ROC) curve analyses were performed. The diagnostic performance of clinical and hematochemical variables was evaluated with parameters, including the area under curve (AUC, >0.700), $p$ value (<0.05), sensitivity and specificity (>70%). Statistical significance was regarded as $p < 0.05$.

# 3 Results

## 3.1 Physical examination findings

Clinical and hematological examinations revealed that 13 of the cats in the Panleukopenia group had sepsis (13 out of 30, 43%). Mental status change was more evident in cats with septic FP (mostly unable to stand but alert, $n$: 9; or unable to stand, apathetic, $n$: 4). Of the palpable lymph nodes, swelling was evident in all cats with FP, mainly in the submandibular and popliteal nodules. No remarkable finding was detected in abdominal palpation. As a result of physical examination, when healthy, septic, and non-septic panleukopenic cats were evaluated together, the body temperature was highest in septic panleukopenic cats ($p < 0.009$). Compared with the healthy cats, all of the panleukopenic cats had higher respiratory rate, mental status, and qSOFA scores ($p = 0.000$) and lower SBP values ($p = 0.000$). In the comparison of septic and non-septic panleukopenic cats, no statistical difference was found in other parameters ($p > 0.05$) except body temperature ($p = 0.000$). Within the scope of qSOFA scoring, it was determined that all cats with FP had a respiratory rate of >22 breaths/min, 15 out of 30 had an SBP of <100 mmHg, and 18 out of 30 were able to stand with assistance, alert but stagnant. Physical examination findings and qSOFA scores are presented in Tables 1 and 2, and qSOFA score evaluation is presented in Table 3.

## 3.2 Hemogram analysis findings

As a result of hemogram analysis, it was observed that WBC, lymphocyte, granulocyte, monocytes, RBC, and hemoglobin levels of the septic panleukopenic cats were lower compared with the healthy cats ($p < 0.016$). WBC, lymphocyte, granulocyte, RBC, and hemoglobin levels were lower in non-septic panleukopenic cats compared with the healthy ones ($p < 0.030$). In septic panleukopenic cats, monocyte and MCH were determined to be lower ($p < 0.048$). No statistical difference was determined in other parameters. Hemogram analysis results are presented in Tables 4 and 5.

**Table 1:** Physical examination findings and qSOFA scores

| Parameters | Control group ($n$: 10) median (min–max) | Panleukopenia group ($n$: 30) median (min–max) | |
|---|---|---|---|
| | | Septic FP ($n$: 13) | Non-septic FP ($n$: 17) |
| Heart rate (beats/min) | 120 (110–134) | 128 (106–144) | 120 (100–152) |
| Body temperature (rectal, °C) | 38.6 (38.2–39.2) | 39.9 (39.7–40.5) | 39.1 (38.3–39.6) |
| CRT (s) | 2 (2–3) | 3 (1–4) | 2 (1–4) |
| Respiratory rate (breaths/min) | 33 (22–44) | 66 (56–92) | 72 (58–90) |
| Systemic blood pressure (mmHg) | 125 (120–134) | 102 (90–122) | 100 (88–112) |
| Mental state (ranging from 1 to 3) | 0 (0–0) | 3 (2–4) | 2 (2–4) |
| qSOFA (ranging from 1 to 3) | 1 (1–1) | 2 (2–3) | 2 (2–3) |

qSOFA – quick Sepsis-related Organ Failure Assessment.

**Table 2:** *p* Values of intergroup comparison of physical examination findings and qSOFA scores (*p* value <0.05: bold)

| Parameters | *p* Values | | |
|---|---|---|---|
| | Control vs septic FP | Control vs non-septic FP | Septic FP vs non-septic FP |
| Heart rate (beats/min) | 0.291 | 0.801 | 0.508 |
| Body temperature (rectal, °C) | **0.000** | **0.009** | **0.000** |
| CRT (s) | 0.356 | 0.973 | 0.496 |
| Respiratory rate (breaths/min) | **0.000** | **0.000** | 0.321 |
| Systemic blood pressure (mmHg) | **0.000** | **0.000** | 0.657 |
| Mental state (ranging from 1 to 3) | **0.000** | **0.000** | 0.097 |
| qSOFA (ranging from 1 to 3) | **0.000** | **0.000** | 0.380 |

qSOFA – quick Sepsis-related Organ Failure Assessment.

**Table 3:** qSOFA criteria and scoring

| Parameters | Distribution (%) |
|---|---|
| Respiratory rate >22 breathgs/min | 30 out of 30 (100) |
| Systemic blood pressure <100 mmHg | 15 out of 30 (50) |
| Mental state | = 2; 18 out of 30 (60) |
| | = 3; 12 out of 30 (40) |

## 3.3 Serum biochemistry profiling findings

As a result of serum biochemistry profiling, septic panleukopenic cats had higher BUN, creatinine, ALT, LDH, total bilirubin, and CRP levels compared with the healthy cats ($p < 0.033$). Non-septic panleukopenic cats also had higher BUN, creatinine, AST, ALT, LDH, phosphorus,

**Table 4:** Hemogram analysis results

| Parameters | Control group (*n*: 10) median (min–max) | Panleukopenia group (*n*: 30) median (min–max) | |
|---|---|---|---|
| | | Septic FP (*n*: 13) | Non-septic FP (*n*: 17) |
| WBC ($\times 10^9$ cells/L) | 10.75 (5.39–18.03) | 2.48 (0.33–8.04) | 3.55 (0.4–10.29) |
| Lym ($\times 10^9$ cells/L) | 4.12 (1.93–9.47) | 1.6 (0.26–4.74) | 1.89 (0.32–5.21) |
| Gran ($\times 10^9$ cells/L) | 4.6 (2.16–8.49) | 0.59 (0.03–6.62) | 0.6 (0.01–3.4) |
| Mon ($\times 10^9$ cells/L) | 0.79 (0.2–2.44) | 0.14 (0.01–0.99) | 0.48 (0.03–2.33) |
| RBC ($m/mm^3$) | 8.64 (3.24–12.7) | 5.8 (3.33–9.6) | 5.5 (3.52–12.83) |
| MCV (fl) | 45.6 (36.5–66.6) | 48.9 (37.7–73.7) | 47.9 (36.1–77.8) |
| MCH (pg) | 13.15 (10.2–28) | 13.2 (7.2–17.1) | 14.5 (12.1–23.2) |
| MCHC (g/dL) | 29 (23.9–42.3) | 25.3 (16.7–36.1) | 29.2 (19.3–36.8) |
| Hb (g/dL) | 12.7 (9.1–14.7) | 8.1 (3.8–12.7) | 9 (5.4–17.4) |

WBC – leukocyte, Lym – lymphocyte, Gran – granulocyte, Mon – monocyte, RBC – erythrocyte, MCV – mean corpuscular volume, MCH – mean corpuscular hemoglobin, MCHC – mean corpuscular hemoglobin concentration, Hb – hemoglobin.

**Table 5:** *p* Values of intergroup comparison of hemogram analysis results ($p < 0.05$: bold)

| Parameters | *p* Values | | |
|---|---|---|---|
| | Control vs septic FP | Control vs non-septic FP | Septic FP vs non-septic FP |
| WBC ($\times 10^9$ cells/L) | **0.000** | **0.000** | 0.716 |
| Lym ($\times 10^9$ cells/L) | **0.005** | **0.006** | 0.785 |
| Gran ($\times 10^9$ cells/L) | **0.001** | **0.000** | 0.765 |
| Mon ($\times 10^9$ cells/L) | **0.016** | 0.425 | **0.039** |
| RBC ($m/mm^3$) | **0.004** | **0.030** | 0.269 |
| MCV (fl) | 0.248 | 0.183 | 0.896 |
| MCH (pg) | 0.427 | 0.639 | **0.048** |
| MCHC (g/dL) | 0.146 | 0.930 | 0.106 |
| Hb (g/dL) | **0.000** | **0.023** | 0.242 |

WBC – leukocyte, Lym – lymphocyte, Gran – granulocyte, Mon – monocyte, RBC – erythrocyte, MCV – mean corpuscular volume, MCH – mean corpuscular hemoglobin, MCHC – mean corpuscular hemoglobin concentration, Hb – hemoglobin.

total bilirubin, and CRP levels compared with the healthy ones ($p < 0.032$). In septic panleukopenic cats, only albumin level was determined to be lower ($p < 0.032$). No statistical difference was determined in other parameters. Serum biochemistry analysis results are presented in Tables 6 and 7.

## 3.4 Spearman's rank correlation coefficient test results

Spearman's correlation test result revealed positive very strong correlations between WBC and lymphocyte (rs: 0.832), WBC and granulocyte (rs: 0.816); positive strong correlations between WBC and monocytes (rs: 0.712), lymphocyte and monocytes (rs: 0.653), hemoglobin and RBC (rs: 0.762), and LDH and BUN (rs: 0.603). When all parameters were taken into account, CRP was the only parameter with which the qSOFA score showed a significant correlation and its strength was determined to be positively strong (rs: 0.687). Spearman's correlation test results are presented in the Supplementary file.

## 3.5 ROC analysis

ROC analysis revealed that body temperature (AUC: 1.000), WBC (AUC: 0.967), and granulocyte counts (AUC: 0.937)

**Table 6:** Serum biochemistry profiling

| Parameters | Control group (*n*: 10) median (min–max) | Panleukopenia group (*n*: 30) median (min–max) | |
|---|---|---|---|
| | | Septic FP (*n*: 13) | Non-septic FP (*n*: 17) |
| BUN (mg/dL) | 16.2 (5.1–20.6) | 33.4 (19.6–86) | 30.4 (10.1–114.4) |
| Crea (mg/dL) | 0.75 (0.5–1.2) | 2.3 (0.7–8.1) | 2.4 (0.4–25.1) |
| AST (U/L) | 26.5 (15–55) | 53 (20–372) | 50 (17–161) |
| ALT (U/L) | 34 (16–76) | 70 (19–118) | 54 (19–184) |
| ALP (U/L) | 37.5 (12–169) | 22 (13–116) | 42 (4–270) |
| LDH (U/L) | 101 (38–198) | 205 (93–1,429) | 367 (52–750) |
| Phosphorous (mg/dL) | 5.55 (2.8–7.3) | 6.1 (4.2–9.3) | 6.6 (2.8–14.4) |
| Cholesterol (mg/dL) | 143.5 (103–213) | 153 (107–237) | 183 (105–431) |
| Total bilirubin (mg/dL) | 0.4 (0.1–1.1) | 0.9 (0.4–2.3) | 1.1 (0.3–3.9) |
| Albumin (g/dL) | 2.9 (2.6–3.7) | 2.6 (1.4–3.7) | 3.2 (2.2–4.6) |
| Total protein (g/dL) | 6.5 (5.4–7.5) | 7.3 (4.2–11) | 7.3 (4.7–12.9) |
| CRP (mg/L) | 0.2 (0.1–0.2) | 0.6 (0.3–1.8) | 0.8 (0.3–2.1) |

BUN – blood urea nitrogen, Crea – creatinine, AST – aspartate aminotransferase, ALT – alanine transaminase, ALP – alkaline phosphatase, LDH – lactate dehydrogenase, CRP – C-reactive protein.

**Table 7:** *p* Values of intergroup comparison of serum biochemistry profiling results ($p < 0.05$: bold)

| Parameters | *p* Values | | |
|---|---|---|---|
| | Control vs septic FP | Control vs non-septic FP | Septic FP vs non-septic FP |
| BUN (mg/dL) | **0.001** | **0.003** | 0.355 |
| Crea (mg/dL) | **0.002** | **0.032** | 0.570 |
| AST (U/L) | 0.052 | **0.022** | 0.220 |
| ALT (U/L) | **0.007** | **0.012** | 0.958 |
| ALP (U/L) | 0.504 | 0.568 | 0.247 |
| LDH (U/L) | **0.033** | **0.000** | 0.880 |
| Phosphorous (mg/dL) | 0.198 | **0.020** | 0.191 |
| Cholesterol (mg/dL) | 0.400 | 0.072 | 0.263 |
| Total bilirubin (mg/dL) | **0.004** | **0.001** | 0.590 |
| Albumin (g/dL) | 0.193 | 0.250 | **0.032** |
| Total protein (g/dL) | 0.374 | 0.083 | 0.573 |
| CRP (mg/L) | **0.000** | **0.000** | 0.293 |

BUN – blood urea nitrogen, Crea – creatinine, AST – aspartate aminotransferase, ALT – alanine transaminase, ALP – alkaline phosphatase, LDH – lactate dehydrogenase, CRP – C-reactive protein.

had excellent efficacy, RBC value (AUC: 0.817) had good efficacy, mental state evaluation (AUC: 0.798) and CRP level (AUC: 0.793) had fair diagnostic efficacy for detecting the presence of sepsis in panleukopenic cats. ROC analysis results of clinical findings are presented in Table 8; ROC analysis results of hemogram findings are presented in Table 9; and ROC analysis results of serum biochemistry findings are presented in Table 10. In addition, ROC curves of clinical findings, hemogram and serum biochemistry parameters are presented in Figure 1(a–c), respectively.

# 4 Discussion

FP is a fatal, highly contagious, viral disease of cats caused by FPV with the peculiar clinical and hematological alterations [19]. Early detection of FP with accurate testing methods including point-of-care tests and routine laboratory analyses such as hematochemical profiling is very important to identify infected cats as the disease increases susceptibility to the development of organ dysfunction, sepsis, and DIC. In the present study, it was determined that sepsis developed in 43% of the panleukopenic cats along with significant clinical and hematochemical alterations such as elevated body temperature, altered mental state, leukopenia, hypoalbuminemia, and high CRP levels ($p < 0.05$). Also, it was observed that the qSOFA score was strongly (positive) correlated only with the serum CRP level, although it could not differentiate the septic cats from the non-septic panleukopenic ones ($p > 0.293$).

The most common presentation of FP is characterized by an acute course of disease over several days with fever, lethargy, anorexia, vomiting, diarrhea, and severe dehydration. Only some of these signs may be present, vomiting usually precedes diarrhea, and in contrast to dogs with parvoviral enteritis, hemorrhagic diarrhea is much less common, ranging from 3 to 15% of cats with

**Table 8:** Clinical examination findings and qSOFA score

| Parameter | AUC | Std. error | *p* Value | Asymp. 95% CI | | Cut-off | Sensitivity (%) | Specificity (%) |
|---|---|---|---|---|---|---|---|---|
| | | | | Lower bound | Upper bound | | | |
| Heart rate (beats/min) | 0.603 | 0.099 | 0.299 | 0.409 | 0.796 | 119 | 76.9 | 40.7 |
| **Body temperature (rectal, °C)** | **1.000** | **0.000** | **0.000** | **1.000** | **1.000** | **39.65** | **100** | **100** |
| CRT (s) | 0.578 | 0.094 | 0.427 | 0.394 | 0.763 | 2.5 | 53.8 | 56.6 |
| Respiratory rate (breaths/min) | 0.613 | 0.088 | 0.254 | 0.440 | 0.785 | 59 | 84.6 | 44.4 |
| Systemic blood pressure (mmHg) | 0.352 | 0.089 | 0.133 | 0.177 | 0.527 | 101 | 53.8 | 33.3 |
| **Mental state (ranging from 1 to 3)** | **0.798** | **0.071** | **0.003** | **0.658** | **0.937** | **2.5** | **92.3** | **74.1** |
| qSOFA (ranging from 1 to 3) | 0.634 | 0.086 | 0.175 | 0.465 | 0.803 | 2.5 | 30.8 | 69.4 |

qSOFA – quick Sepsis-related Organ Failure Assessment, AUC – area under curve, Std. Error – standard error, CI – confidence interval.
Bold rows indicate statistical significance.

**Table 9:** Hemogram findings

| Parameter | AUC | Std. error | *p* Value | Asymp. 95% CI | | Cut-off | Sensitivity (%) | Specificity (%) |
|---|---|---|---|---|---|---|---|---|
| | | | | Lower bound | Upper bound | | | |
| **WBC ($\times 10^9$ cells/L)** | **0.967** | **0.026** | **0.000** | **0.916** | **1.000** | **5.37** | **100** | **80** |
| Lym ($\times 10^9$ cells/L) | 0.853 | 0.061 | 0.001 | 0.734 | 0.973 | 1.91 | 100 | 60 |
| **Gran ($\times 10^9$ cells/L)** | **0.937** | **0.037** | **0.000** | **0.865** | **1.000** | **2.02** | **100** | **83.3** |
| Mon ($\times 10^9$ cells/L) | 0.725 | 0.081 | 0.035 | 0.565 | 0.885 | 0.39 | 90 | 56.7 |
| **RBC ($m/mm^3$)** | **0.817** | **0.096** | **0.003** | **0.628** | **1.000** | **6.97** | **90** | **80** |
| MCV (fl) | 0.405 | 0.097 | 0.373 | 0.216 | 0.594 | 45.25 | 60 | 40 |
| MCH (pg) | 0.435 | 0.114 | 0.542 | 0.212 | 0.658 | 14.3 | 40 | 53.3 |
| MCHC (g/dL) | 0.562 | 0.101 | 0.563 | 0.365 | 0.759 | 27.9 | 70 | 46.7 |
| Hb (g/dL) | 0.822 | 0.065 | 0.003 | 0.694 | 0.950 | 9.05 | 100 | 63.3 |

WBC – leukocyte, Lym – lymphocyte, Gran – granulocyte, Mon – monocyte, RBC – erythrocyte, MCV – mean corpuscular volume, MCH – mean corpuscular hemoglobin, MCHC – mean corpuscular hemoglobin concentration, Hb – hemoglobin, AUC – area under curve, Std. Error – standard error, CI – confidence interval.
Bold rows indicate statistical significance.

**Table 10:** Serum biochemistry findings

| Parameter | AUC | Std. error | *p* Value | Asymp. 95% CI | | Cut-off | Sensitivity (%) | Specificity (%) |
|---|---|---|---|---|---|---|---|---|
| | | | | Lower bound | Upper bound | | | |
| BUN (mg/dL) | 0.591 | 0.091 | 0.331 | 0.412 | 0.770 | 22 | 76.5 | 41.8 |
| Crea (mg/dL) | 0.634 | 0.096 | 0.151 | 0.447 | 0.822 | 2.05 | 70.6 | 65.2 |
| AST (U/L) | 0.529 | 0.096 | 0.753 | 0.341 | 0.717 | 44 | 58.8 | 56.5 |
| ALT (U/L) | 0.606 | 0.092 | 0.256 | 0.426 | 0.787 | 41.5 | 70.6 | 52.2 |
| ALP (U/L) | 0.526 | 0.099 | 0.784 | 0.332 | 0.719 | 25.5 | 64.7 | 47.8 |
| LDH (U/L) | 0.670 | 0.092 | 0.069 | 0.490 | 0.850 | 163.5 | 70.6 | 47.8 |
| Phosphorus (mg/dL) | 0.706 | 0.087 | 0.028 | 0.534 | 0.877 | 6.15 | 82.4 | 65.2 |
| Cholesterol (mg/dL) | 0.646 | 0.090 | 0.119 | 0.469 | 0.823 | 149.5 | 70.6 | 47.8 |
| Total bilirubin (mg/dL) | 0.712 | 0.083 | 0.023 | 0.550 | 0.874 | 0.6 | 88.2 | 56.5 |
| Albumin (g/dL) | 0.662 | 0.090 | 0.082 | 0.485 | 0.840 | 2.95 | 70.6 | 59.9 |
| Total protein (g/dL) | 0.624 | 0.092 | 0.185 | 0.443 | 0.805 | 7.2 | 64.7 | 59.9 |
| **CRP (mg/L)** | **0.793** | **0.072** | **0.002** | **0.651** | **0.935** | **0.65** | **82.4** | **73.9** |

BUN – blood urea nitrogen, Crea – creatinine, AST – aspartate aminotransferase, ALT – alanine transaminase, ALP – alkaline phosphatase, LDH – lactate dehydrogenase, CRP – C-reactive protein, AUC – area under curve, Std. error – standard error, CI – confidence interval. Bold rows indicate statistical significance.

FP [7]. The clinical signs of FP are most severe in cats less than 6 months of age [2]. As previously reported, adult cats generally manifest a transient fever and depression. Also, especially in kittens less than 2 months old, disease can be peracute, resulting in sudden death from septic shock with no premonitory signs [18]. The most common clinical findings identified in the cats with FP in the present study were fever (*n*: 22, 73%), lethargy (*n*: 21, 70%), anorexia (*n*: 30, 100%), vomiting (*n*: 14, 47%), diarrhea (*n*: 11, 37%), and severe dehydration (*n*: 19, 63%). These findings were more severe in the cats less than 6 months old (all findings were present in 13 of 30 panleukopenic cats, 43%) of the present study. Considering the epidemiological data of the panleukopenic cats of the present study, the severity of the clinical findings may be related to early age, being unvaccinated, and immunity gap [3]. Also, the lower respiratory rate ($p = 0.000$) of the septic panleukopenic cats compared with non-septic ones may be related to compromised respiratory reflex due to the development of sepsis, and fever may be associated with secondary infections due to transient immunosuppression [14]. Moreover, the fact that no difference was detected in the CRT and heart rate values between the groups ($p > 0.05$) supports the fact that hemodynamic changes in septic cats are different from the classical sepsis manifestation, which is frequently accompanied by a hyperdynamic phase [13,14]. In the ROC analysis, which was performed to investigate the presence of sepsis in panleukopenic cats, it was observed that the body temperature value had excellent performance (AUC: 1.000) and the mental state evaluation (AUC: 0.798) had good diagnostic performance. In a previous study, it was reported that subtle changes in body temperature patterns may be an early indicator of sepsis [20]. As the rectal temperature in healthy cats can reach 39.3°C in the veterinary consultation room due to stress, it was observed that a cut-off value of 39.6°C of the present study was related to infection/inflammation [6]. It is a fact that sepsis is often characterized by an acute brain dysfunction associated with increased morbidity and mortality. In the majority of panleukopenic cats (60%) of the present study, mental status was characterized by being able to stand with assistance and environmentally sensitive but stagnant. These findings may be related to excessive microglial activation, impaired cerebral perfusion, blood–brain-barrier dysfunction, and altered neurotransmission caused by panleukopenia [21,22].

Following the orofecal transmission, viral replication in oropharyngeal lymphoid tissue occurs within 18–24 h and viremia can be detected within 2–7 days post-infection. Clinical disease occurs after an incubation period of 2–10 days [2]. FPV infects and kills cells that are associated with replication and causes cytopathic effects of rapidly growing and dividing, such as those in the bone marrow, lymphoid cells, and intestines [23]. As the virus infects all tissues, including lymphoid tissue, with cell-free viremia, cellularity decreases [1,2,23]. In most cats, gastrointestinal (GI) signs coincide with severe leukopenia, with early neutropenia from neutrophil losses into the GI tract, followed by leukopenia from bone marrow suppression [7]. In addition, as the GI barrier is often destroyed in panleukopenic cats, intestinal

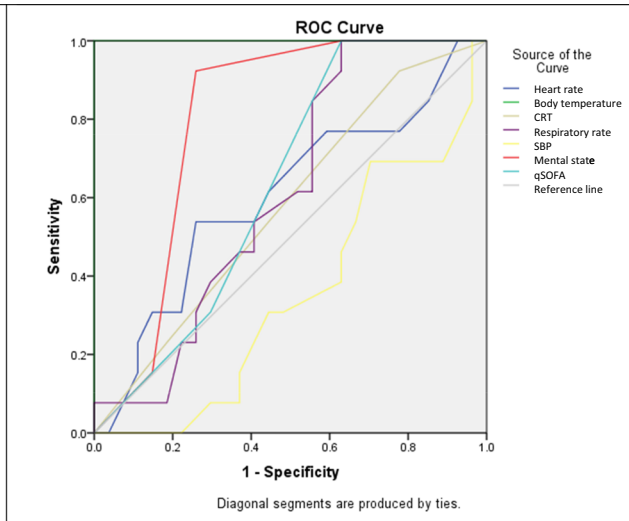
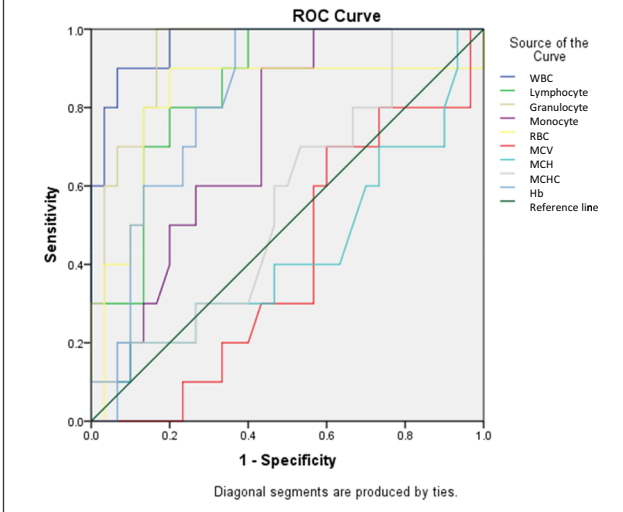
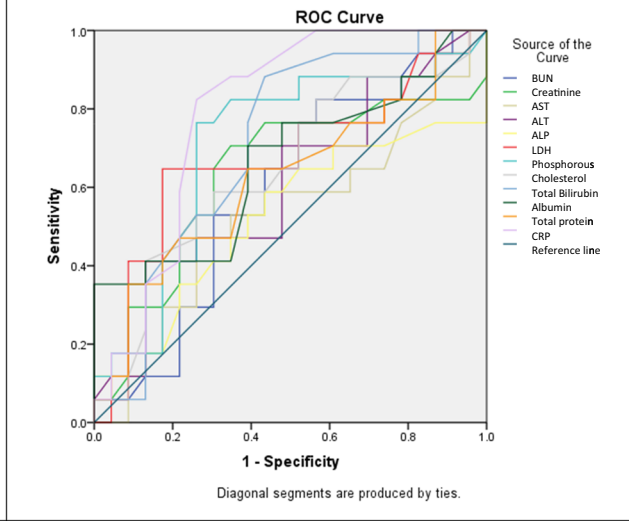
| | |
|---|---|
| ROC curves of physical examination parameters and qSOFA score |  |
| ROC curves of hemogram parameters |  |
| ROC curves of serum biochemistry variables |  |



**Figure 1:** ROC curves of clinical findings, hemogram and serum biochemistry parameters.

bacteria can invade the bloodstream and bacteraemia combined with neutropenia can lead to sepsis in these immunocompromised animals [18]. Thus, abnormal hematological findings such as leukopenia, which is characterized by neutropenia and lymphopenia, are frequently encountered in cats with FP [2,6,9]. In the present study, the panleukopenic cats had lower WBC, lymphocyte, and granulocyte levels than the healthy cats ($p < 0.006$). When considering the presence of sepsis, the monocyte levels of the septic panleukopenic cats were lower than the non-septic ones ($p < 0.039$). The abnormal leukogram patterns detected in the present study can be explained by the direct cytopathic effects of the FPV on the bone marrow. In addition, conditions that contribute to the development of cytopenia, persistent or cyclic neutropenia, and lymphopenia may include thymic atrophy, myelosuppressive syndrome, and depletion of the paracortical regions of the lymph nodes [22]. Also, leukopenia which is not generally considered a normal response to infection could be as a sign of sepsis-defining hematological organ dysfunction within the Sepsis-3 framework [24]. Several mechanisms such as increased use in tissue, bone marrow damage, lack of neutrophil production, and sequestration of neutrophils as a result of endotoxemia are reported for the development of neutropenia in FP [6]. During septic conditions, neutrophils experience highly dysregulated functions such as recruitment of immature cells, impaired migration, inefficient pathogen recognition, and tissue damage [25]. In addition to the notorious effects of neutropenia, monocytopenia also contributes to the increased risk of mortality, bacteremia rate, myelotoxicity, and development of organ dysfunction, especially in septic patients [6]. In the septic panleukopenic cats of the present study, monocytopenia was possibly due to the relative lack of monocytopoiesis related to septic insults [26]. In previous studies, it was reported that the presence of neutropenia, monocytopenia, lymphopenia, and leukopenia both at first admission and during hospitalization were prognostic indicators of poor outcome for FP [6]. Although the diagnosis of FP is made by the detection of FP antigen in feces, evaluation of clinical findings and hematochemical abnormalities is essential in the early diagnosis of fatal complications associated with FP rather than diagnosis [18]. In the ROC analysis of the hemogram parameters in the present study, WBC (AUC: 0.967) and granulocyte (AUC: 0.937) values were found to have excellent diagnostic performance in detecting the presence of sepsis. As the cytopenias during sepsis may result from decreased bone marrow production or increased destruction, evaluation of these parameters can help both the diagnosis of sepsis/sepsis-related possible complications and the prediction of prognosis.

Anemia is commonly associated with feline inflammatory diseases, and its pathogenesis in cats with sepsis is complex and multifactorial [13]. It was reported that anemia occurs in 50% of FP cases and is usually mild due to the long lifespan of erythrocytes unless there is severe GI blood loss [2]. Nevertheless, non-regenerative anemia is a common finding for FP [8]. In the present study, it was determined that the panleukopenic cats had lower RBC and Hb levels compared with the healthy cats ($p < 0.030$). As a result of the comparison based on the presence of sepsis, MCH levels of the septic panleukopenic cats were lower than the non-septic ones ($p < 0.048$). These findings may be associated with the suppression of bone marrow, immune system, and inflammation due to opportunistic infections. Other possible mechanisms causing lower RBC, Hb, and MCH levels are structural changes of the bone marrow due to cytokines or direct cytopathic effects of the FPV [27]. Good diagnostic performance of RBC (AUC: 0.817) value, which was determined as a result of the ROC analysis, along with the fact that erythrocytes are very sensitive to sepsis-related damage [28], may provide an early warning signal of sepsis and are a factor in the microvascular dysfunction that has been associated with organ dysfunction. Therefore, these findings should be evaluated and must be considered as severe complications that affect the prognosis of FP [16].

Biochemical abnormalities such as azotemia, increased serum activities of AST or ALT, or hyperbilirubinemia are typically non-specific in cats with FP [22]. Icterus is rare. However, hypoalbuminemia, which is considered a negative prognostic indicator, is the most common abnormality detected and usually occurs due to decreased protein intake and increased GI losses. Azotemia can occur from prerenal causes, such as dehydration [18,27]. It is reasonable to speculate that frequent feline viral rhinotracheitis/calicivirus/panleukopenia vaccinations in cats might induce antibodies that bind to kidney tissues, leading to kidney diseases characterized by azotemia [29]. Nevertheless, it is well established that the kidney is a commonly affected organ during sepsis, and its involvement carries a high mortality risk. The pathophysiology of kidney injury in sepsis is complex and multi-factorial and includes intrarenal hemodynamic changes, endothelial dysfunction, infiltration of inflammatory cells in the renal parenchyma, intraglomerular thrombosis, and obstruction of tubules with necrotic cells and debris [30]. Therefore, elevated BUN and creatinine levels ($p < 0.003$) of the panleukopenic cats of the present study may be associated with hypoperfusion due to dehydration and anorexia, since all of the cats included in the study were unvaccinated.

The liver enzymes such as ALT and AST are sensitive indicators of liver disease or injury but are not specific and do not offer any precise indication of liver functionality. In cats, even a small increase in ALT is considered an indicator of liver injury, due to the limited serum half-life of ALT, and an increase in AST could imply significant liver injury, due to its mitochondrial localization [31]. During the course of sepsis, the liver contributes actively to host defense and tissue repair through crosstalk between hepatic cells and blood cells. Hepatocytes will shift their metabolic pathway toward upregulation of the inflammatory response, which is responsible for an increase in the synthesis of acute-phase proteins mediated predominantly by interleukin 6 [32]. This shift leads to increases in cytokines such as CRP and decreases in albumin. Also, the metabolic changes and inflammatory response lead to a decrease in biotransformation liver function, especially a reduction in cytochrome P450 activity. As the feline liver is susceptible to disease and has limited conjugation capabilities, in addition to the adhesion of neutrophils to sinusoidal endothelial cells, promoting thrombi formation in the sinusoids and impairing liver microvascular perfusion, limited protein intake cause and worsen the hepatic injury [33]. For this reason, although the elevated AST, ALT, and total bilirubin levels ($p < 0.022$) of the panleukopenic cats in the present study can be associated with hepatic function loss, FPV-related gastroenteritis causing diarrhoea, dehydration, malnutrition, and circulatory and metabolic dysfunction can contribute to the elevation of the aforementioned parameters [34].

Decreased albumin levels ($p < 0.032$) of the septic panleukopenic cats compared with the non-septic panleukopenic cats may be associated with hepatic dysfunction as well as decreased protein intake and increased GI losses [27]. In addition, the severity of hypoalbuminemia in sepsis may increase as a result of downregulated hepatic production and leak through a damaged endothelial barrier due to FPV-related gastroenteritis [13]. Therefore, assessment of kidney and liver parameters may help to evaluate the prognosis by providing information about the severity of pathological changes that increase mortality. It is a well-known fact that critical illness predisposes patients to serum phosphate disturbances. Even though hypophosphatemia may develop as a result of decreased intake or absorption, increased renal excretion, hyperphosphatemia occurs as a consequence of renal dysfunction, hemolysis, rhabdomyolysis, or lactic ketoacidosis [35]. In the present study, the statistically significantly higher phosphorus levels of non-septic panleukopenic cats compared with the healthy cats and the numerically higher phosphorus levels of septic panleukopenic cats compared with the healthy ones, may be associated with lactic ketoacidosis due to renal dysfunction and anorexia, considering the results of the related biochemical parameters [27,35].

CRP, a positive acute phase protein (APP), is synthesized primarily in liver hepatocytes and its concentration increases during inflammatory events [36]. It is an acute marker for inflammation, and its levels have been shown to increase in several diseases, including sepsis and viral and bacterial infections [37]. In studies conducted in dogs with parvoviral enteritis, it was reported that CRP level was higher in non-survivor dogs, and higher CRP level was associated with increased mortality [38,39]. In the present study, elevated CRP levels ($p = 0.000$) of the panleukopenic cats compared with the healthy cats were associated with the host's acute phase response to FPV. The acute phase response is highly non-specific because it develops secondary to numerous conditions such as infection and trauma that can produce tissue injury. In addition, it was reported that production and response of APPs vary depending on the species. For example, in the dog, a strong response occurs with CRP; however, in cats, significant increases of CRP have not been detected after an inflammatory stimulus [40]. In line with these data, the elevated CRP levels of the panleukopenic cats of the present study and the strong positive correlation with the qSOFA score (rs: 0.687) can be associated with the fact that FPV is an important pathogen that strongly stimulates the immune system (considering that the time of onset of symptoms and admission to hospital of the present study is between 1 and 3 days) and causes multiple organ damage [41]. CRP, which was determined to have a fair diagnostic performance (AUC: 0.793) in the ROC analysis, can be used for diagnostic and prognostic purposes for sepsis in panleukopenic cats, especially in triage, since its level increases 2 h after the triggering event and peaks at 48 h [42].

Fundamentally, the host immune response is designed to localize, confine, and destroy pathogens while repair mechanisms are activated. Sepsis is a dysregulated form of this response, and alterations can manifest as endothelial cell damage, coagulopathies, microcirculatory and hemodynamic alterations, metabolic and neuroendocrine immune network abnormalities, endoplasmic reticulum stress, autophagy, and many other pathophysiological processes leading to vascular leakage and organ failure [15]. As the incubation period of FPV infection is 2–14 days, exposed cats that are clinically healthy but incubating the infection might not show clinical signs until days after they have arrived at a shelter or an adoptive home [43]. For this reason, quick clinical evaluation/

scoring along with routine hematochemical parameters can help in early diagnosis of possible fatal complications related to FP. In addition, clinical and laboratory evaluations are even more important in critical feline diseases, as feline sepsis differs from classic hemodynamic changes [13]. Although there are studies evaluating the effectiveness of qSOFA scoring in critically ill dogs [44], no study has been found that evaluated qSOFA score in naturally developed FP cases, which is an important sepsis model. In the present study, as a result of qSOFA evaluation, it was determined that the panleukopenic cats had lower SBP value ($p = 0.000$), respiratory rate ($p = 0.000$), mental status ($p = 0.000$), and total qSOFA scores ($p = 0.000$) compared with the healthy cats. Although the qSOFA score was observed to be insufficient to distinguish between septic and non-septic panleukopenic cats, it may have clinical prognostic value when evaluated together with serum CRP level [15].

FP has noticeably worse prognosis than CPV enteritis [29]. Outbreaks can result in high mortality, euthanasia, and shelter closures. Rapid and accurate diagnosis is therefore essential, but this remains a challenge due to a wide variety of clinical findings and false positive test fecal antigen results after vaccination with MLV for at least 14 days [10]. In addition, PCR results are obtained after a waiting period of 1–3 days [17]. For this reason, further prospective investigations are warranted in cats, because, in the retrospective feline study, the mortality rate was high (80%) and cats that died before completion of the 3-day course of therapy were included in the analyses [9]. Thus, together with the physical and laboratory examinations mentioned above, qSOFA evaluation, which can be performed quickly at the bedside, besides the ICU, can provide important diagnostic and prognostic information for the development of FPV-related complications in multi-cat households or shelters, and may enable early treatment interventions.

This study has some limitations. The first is the wide age range of the cats included in the study (1–11 months), which can cause variation in clinical findings. The second is the low number of animals due to the fact that the panleukopenic cats of the present study consist of the cats which were admitted to the animal hospital for diagnosis/treatment purposes. Therefore, investigating the aforementioned parameters and correlations in a cat population with a similar nutritional status and habitat with a larger number of animals may better demonstrate the diagnostic and prognostic efficacy of the qSOFA score together with the hematochemical variables.

Septic cats often present with a very different clinical manifestation than non-septic dogs. This can make rapid recognition of the septic cat challenging. Rapid identification of these patients and determination of the underlying cause are essential for the outcome of these cases. Initial diagnostics in these cases generally consist of a hemogram analysis and serum biochemistry profiling. Although often frustrating, these cases can also be rewarding. Therefore, it was concluded that although the qSOFA score evaluation is not sufficient to distinguish sepsis in cats, unlike dogs, in order to both protect the cat population and achieve a positive clinical outcome, when evaluated together with the aforementioned hematochemical variables, it may help in making early diagnosis of complications such as disease-related organ failure, deciding to initiate appropriate vaccination programs and isolation protocols in panleukopenic cats.

**Acknowledgments:** The authors thank to their faculties and institutes.

**Funding information:** The authors state no funding involved.

**Author contributions:** EG and BBE conceived and designed this study. EG, BBE, and MO conducted the systematic literature review. EG and MS conducted the meta-analyses. EG and MO reported findings from the review and analyses. EG and BBE drafted the manuscript and all other authors revised it critically for important intellectual content. All authors read and approved the final article.

**Conflict of interest:** The authors state no conflict of interest.

**Data availability statement:** All data generated or analyzed during this study are included in this published article

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