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ORIGINAL ARTICLE

Anemia measurements to distinguish between viral and bacterial infections in the emergency department

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Abstract

The clinical diagnosis of acute infections in the emergency department is a challenging task due to the similarity in symptom presentation between virally and bacterially infected individuals, while the use of routine laboratory tests for pathogen identification is often time-consuming and may contain contaminants. We investigated the ability of various anemia-related parameters, including hemoglobin, red cell distribution width (RDW), and iron, to differentiate between viral and bacterial infection in a retrospective study of 3883 patients admitted to the emergency department with a confirmed viral ($n = 1238$) or bacterial ($n = 2645$) infection based on either laboratory tests or microbiological cultures. The ratio between hemoglobin to RDW was found to be significant in distinguishing between virally and bacterially infected patients and outperformed other anemia measurements. Moreover, the predictive value of the ratio was high even in patients presenting with low C-reactive protein values (< 21 mg/L). We followed the dynamics of hemoglobin, RDW, and the ratio between them up to 72 h post emergency department admission, and observed a consistent discrepancy between virally and bacterially infected patients over time. Additional analysis demonstrated higher levels of ferritin and lower levels of iron in bacterially infected compared with virally infected patients. The anemia measurements were associated with length of hospital stay, where all higher levels, except for RDW, corresponded to a shorter hospitalization period. We highlighted the importance of various anemia measurements as an additional host-biomarker to discern virally from bacterially infected patients.

Keywords Emergency department · Anemia · Red cell distribution width · Viral infection · Bacterial infection · C-reactive protein

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Introduction

Acute infectious diseases can be caused by viral, bacterial, fungal, and parasitic agents. To accurately distinguish between bacterial and viral infections is one of the main challenges for a physician upon admission to the emergency department (ED). While these should be treated differently, the uncertainty in clinical diagnosis enhances overuse and misuse of antibiotics, which in turn generates antibiotic resistance. Hence, rapid differentiation between the two types of infectious agents is extremely important and beneficial for effective treatment.

Various laboratory tests (such as PCR or an immunoglobulin test) are available for the detection of viral infections; however, while these tests are indeed fast and accurate, the threat of bacterial co-infection cannot be dismissed. While microbiological cultures and serology are used for bacterial identification, they are costly, time-consuming, and can occasionally contain contaminants (i.e., positive blood cultures for bacteria that are likely to be contaminants and not a true infection), thus rendering them irrelevant for the ED setting. As a result, other clinical parameters were examined for use as prognostic markers to discern between viral and bacterial infection. These included biological markers such as C-reactive protein (CRP), procalcitonin (PCT), and white blood cell and neutrophil counts [1–5]. These markers, together with clinical assessment, were suggested in order to assist clinicians in revealing the etiology of the disease, but to date, none of these assays are commonly used across ED since they are limited by their sensitivity, for example to specific pathogens or inter-patient variability [6–8].

Anemia of inflammation [9–12] is common among patients admitted to the ED following infection, yet the relevance of this finding in distinguishing between viral and bacterial infections has not yet been established. Anemia is defined as a reduction in hemoglobin (Hb), hematocrit, or red blood cell (RBC) count, all obtained as part of the complete blood count, where Hb is most widely employed. When determining the cause of anemia, RBC indices are evaluated: MCV, MCH, MCHC, and red cell distribution width (RDW). RDW represents the variation in volume and size of RBC in an individual patient. Recent studies have suggested that RDW elevation is associated with inflammation, oxidative stress, and bacteremia [13, 14]. In [13], they showed that the RDW at the onset of bacteremia and after 72 h are independent predictors of mortality in patients with Gram-negative bacteremia. Further, in [14], they demonstrated an association between RDW and hsCRP and ESR, two widely used plasma inflammatory biomarkers, in patients who were successively referred by general practitioners for a routine medical check-up.

In this retrospective study, we aimed to characterize the differences in anemia-related measurements between virally and bacterially infected patients. We suggest that utilizing measurements such as iron and the Hb-to-RDW ratio could be beneficial in distinguishing between infection types. Specifically, the Hb-to-RDW ratio is applicable for diagnosing patients with high ambiguity CRP values (CRP levels < 21 mg/L). We further investigated the kinetics of these measurements and demonstrated their relevance to the length of hospital stay (LOS).

Materials and methods

Study population

This was a retrospective study of patients who were admitted to the Emergency Department of the Sourasky Tel Aviv Medical Center, Israel (a 1450-bed tertiary university-affiliated hospital, serving an urban population of approximately 500,000), between July 2007 and May 2018. The study was reviewed and approved by the Institutional Review Board (number 0491-17).

The study cohort is based on electronic health records and comprised 5164 adult patients (≥ 18 years) who were diagnosed with either a viral infection (confirmed by a positive PCR or an immunoglobulin test) or a bacterial infection (confirmed by a positive culture, positive serology, or bacterial antigen identification).

We excluded 301 patients with positive blood cultures due to suspicion of contamination (either an immunoglobulin test result of *cytomegalovirus* IgM Ab-blood or blood culture result of *diphtheroids spp*, *coagulase-negative staphylococcus*, *Staphylococcus haemolyticus*, *Streptococcus viridans group*, and/or a *Gram-positive bacilli* result). A further 163 patients were excluded due to a co-infection, diagnosed by a positive viral test and a positive blood culture. We further excluded 769 patients who lacked at least two measurements of Hb taken during the first 3 days post ED admission, where the first measurement was taken within the first 5 h post ED admission.

Overall, a total of 2645 patients with a bacterial infection and 1238 patients with a viral infection remained in the study cohort.

Computational analysis

Clinical characteristics of the study cohort were summarized using mean and range. Since anemia measurements are known to be age-related with gender differences, these were either assessed separately or taken as covariates throughout the analysis. Box-Cox transformation was applied to RDW, CRP, Fe, ferritin, and transferrin saturation measurements in order to achieve normal distribution.

Analysis of variance (ANOVA) models were used to examine the effect of disease etiology on various anemia parameters, where age and gender were included in the model as covariates. Pearson's correlation coefficient was also adjusted for age and gender, and the P value was calculated based on the correlation coefficient using t distribution with degrees of freedom equal to the length of the sample minus two.

Multivariate Cox proportional hazards regression was used to evaluate the association between each of the different anemia measurements and LOS. The multivariate models were adjusted for gender and age.

Statistical analyses were conducted with R (version 3.4.0, www.r-project.org). All tests were two-sided and a P value of < 0.05 was considered statistically significant.

Results

Anemia measurements at ED admission

To characterize the differences in anemia-related measurements between virally and bacterially infected patients, we used the electronic medical records of 3883 adult patients who were diagnosed either with a viral or bacterial infection. The diagnosis was confirmed by a positive PCR or an immunoglobulin test for viral infections, and a positive culture, positive serology, or bacterial antigen identification for bacterial infections. A total of 2645 bacterial and 1238 viral patients were included in the study. On average, patients were 76 years old (18–105), 49.7% were male, and bacterial patients were older than viral patients (Table 1).

Since Hb is considered the most reliable indicator of anemia, we examined the Hb concentration at ED admission (Fig. 1a). The median Hb level was below the normal range for both males and females (13.35 g/dL [normal range of 14–17.5 g/dL, average 15.7 g/dL] and 12.4 g/dL [normal range of 12.3–15.3 g/dL, average 13.8 g/dL], respectively). In addition, a strong positive correlation was observed between Hb and hematocrit ($R = 0.97$, $P < 10^{-16}$; Fig. 1b, left) and Hb and RBC counts ($R = 0.85$, $P < 10^{-16}$, Fig. 1b, middle). A negative correlation was encountered between Hb and RDW ($R = -0.43$, $P < 10^{-16}$, Fig. 1b, right).

Differential diagnosis via anemia measurements

Next, we explored the ability of different anemia indicators to separate between virally and bacterially infected patients at ED admission (Fig. 2). Taking into account the gender and age of each patient, we tested each anemia indicator measured in a complete blood count (Table 2). The strongest effect was observed for Hb, hematocrit, RBC, and RDW.

Anemia can result from various causes. In order to address both the severity of anemia and its etiology, we used the ratio between the Hb level and RDW at ED admission as a variable that combined the two measures. The Hb-to-RDW ratio was significantly better at differentiating between viral and bacterial infection than each of the following variables separately: Hb-to-RDW ratio, P value $< 10^{-35}$; Hb, P value $< 10^{-29}$; RDW, P value $< 10^{-18}$. Since anemia is known to be more prevalent in the elderly, we also performed a separate analysis for each of these parameters in the younger (ages 18–65) and older (ages > 65) sub-populations. We found a significant differential diagnosis of the Hb-to-RDW ratio in both sub-populations, with a stronger effect in the older sub-population.

Hb-to-RDW ratio may predict infection type

Interestingly, we found that Hb-to-RDW ratio can help predict the type of infection. A ratio < 0.5 was shown to have a 0.9 positive predicting value for bacterial infection, with a false-positive rate of 0.02.

The median CRP upon ED admission for elderly patients in our study was 67.16 mg/L. For elderly patients with relatively low CRP (calculated as lower quartile, CRP < 21), the Hb-to-RDW ratio had a positive predicting value of 0.85, with a false-positive rate of 0.02. Thus, although only relevant to a minority of bacterial patients (10%), the Hb-to-RDW ratio parameter can be used to determine the type of infection in this group of patients, who have a high rate of uncertain diagnosis.

Changes in anemia measurements over time

Although early results from a blood culture test may arrive within 24 h, obtaining a final diagnosis can take up to 72 h. During this time period, complete blood count tests were repeated at least three times for the majority of patients (86%), and our data suggest that these tests could be used to gain an earlier diagnosis. To that end, we were interested in studying the kinetics of anemia parameters up to 72 h post ED admission (h.p.a.). We analyzed consecutive measurements of Hb, RDW, and the ratio between them, and divided the measurements into five groups according to time of complete blood count (Fig. 3). Overall, Hb levels decreased over time until 24 h.p.a., with the largest disparity being between complete blood count taken at admission and 2 to 12 h.p.a. (Fig. 3a, left). The difference in Hb levels between virally and bacterially infected patients remained significant across all time points, while the greatest difference was seen in measurements taken between 12 and 24 h.p.a. (Fig. 3b, left). Interestingly, in bacterially infected patients, there was a significant increase in Hb levels at 24 h.p.a. that was maintained until 72 h.p.a. This finding was not apparent in virally infected patients.

Table 1 Clinical characteristics of cohort ($n = 3883$)

		Viral patients ($n = 1238$)	Bacterial patients ($n = 2645$)
Age (years)	Median (range)	72.5 ± 20.6 (18–105)	77 ± 19.5 (18–102]
	18–65 (n (%))	473 (38%)	832 (31%)
	> 65 (n (%))	765 (62%)	1817 (69%)
Gender	Male (n (%))	654 (53%)	1277 (48%)
	Female (n (%))	584 (47%)	1372 (52%)

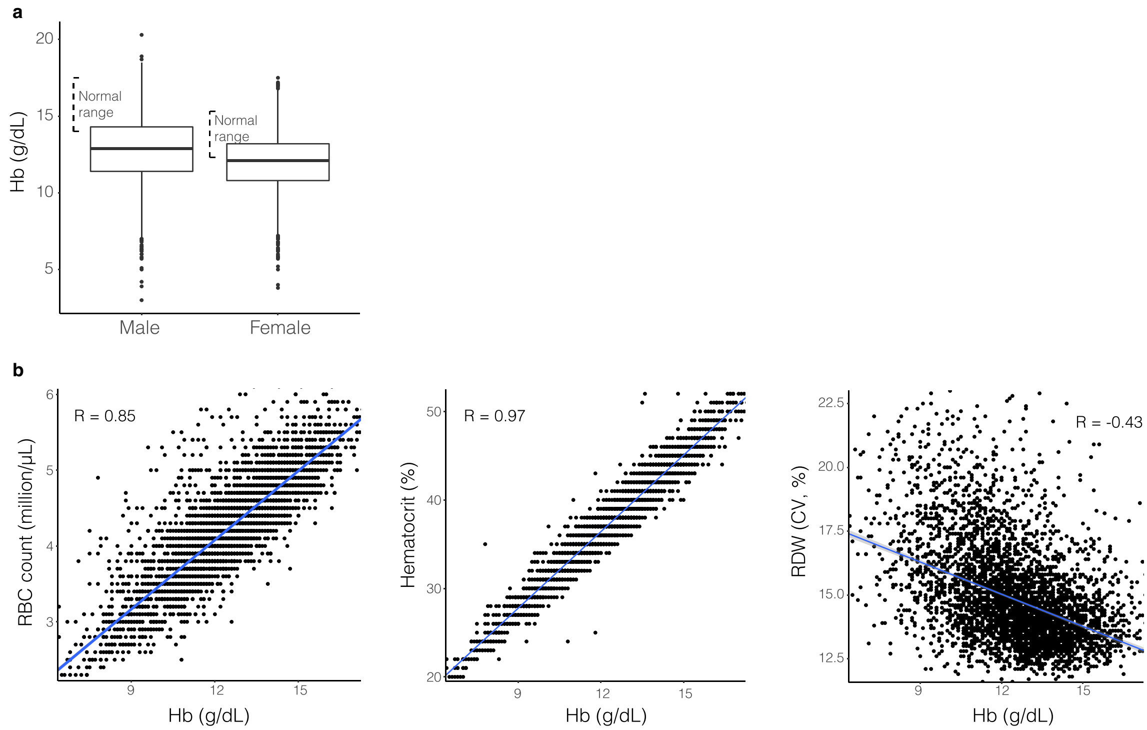

Fig. 1 **a** The majority of patients admitted to the ED following viral or bacterial infection have anemia. Hb levels upon ED admission are shown in boxplots by gender, while the normal range is depicted. Normal range values for Hb were defined as 14.0–17.5 g/dL and 12.3–15.3 g/dL for males and females respectively, with average values of 15.7 g/dL and 13.8 g/dL, respectively. **b** Correlation of Hb (*x*-axis) to various anemia measurements (*y*-axis) upon ED admission—RBC (left), hematocrit (middle), and RDW (right). ED, emergency department; Hb, hemoglobin; RBC, red blood cells; RDW, red cell distribution width

The RDW increased between 2 and 12 h.p.a. and then stabilized (Fig. 3a, middle), while the difference between the means of RDW of virally and bacterially infected patients was maintained over time (Fig. 3b, middle). The Hb-to-RDW ratio decreased between measurements taken at admission and between 2 and 12 h.p.a. (Fig. 3a, right), which remained unchanged thereafter. Here too, the difference between virally and bacterially infected subjects was maintained over time (Fig. 3b, right).

Differential diagnosis via iron measurements

Serum iron measurements are not routinely performed in the ED, but rather during hospitalization and then only for anemic patients. To explore the efficacy of iron measurements, we focused on serum iron tests taken between 12 and 48 h.p.a. In our cohort, these measurements were available for 618 patients where median Hb levels were 10.79 and 10.36 g/dL for males and females, respectively. We found that iron and ferritin levels were significantly different in virally and bacterially infected patients (Fig. 4 and Table 3), with significantly lower levels of iron and higher levels of ferritin in bacterially infected patients.

Anemia measurements and disease characteristics

To gain a better insight into the molecular mechanism, we were interested in the correlation between these different anemia measurements and disease characteristics. To that end, we investigated the correlation between anemia measurements, including iron, and the number of neutrophils as an assessment of stress. As expected, we found a significant correlation between CRP and the number of neutrophils in both virally and bacterially infected subjects ($R = 0.32$, $P < 10^{-60}$). A positive correlation was also found in ferritin, in bacterially infected patients only ($R = 0.11$, $P < 10^{-2}$). A negative correlation in the number of neutrophils was found in Fe and transferrin saturation in both virally ($R = -0.27$, $P < 10^{-11}$ and $R = -0.14$, $P < 0.05$, respectively) and bacterially infected patients ($R = -0.23$, $P < 10^{-8}$ and $R = -0.11$, $P < 0.05$, respectively). A strong negative correlation was observed in MCHC, only in viral-infected patients ($R = -0.19$, $P < 10^{-23}$).

Next, we assessed LOS. In our cohort, 3312 were admitted for a period of less than 30 days, where the median LOS was 6 days (7 and 5 days for bacterially and virally infected patients). We estimated LOS with a Cox regression model taking into account the gender and age of the patients. Each of the anemia measurements was estimated upon admission (except for iron measurements, which were taken between 12 and

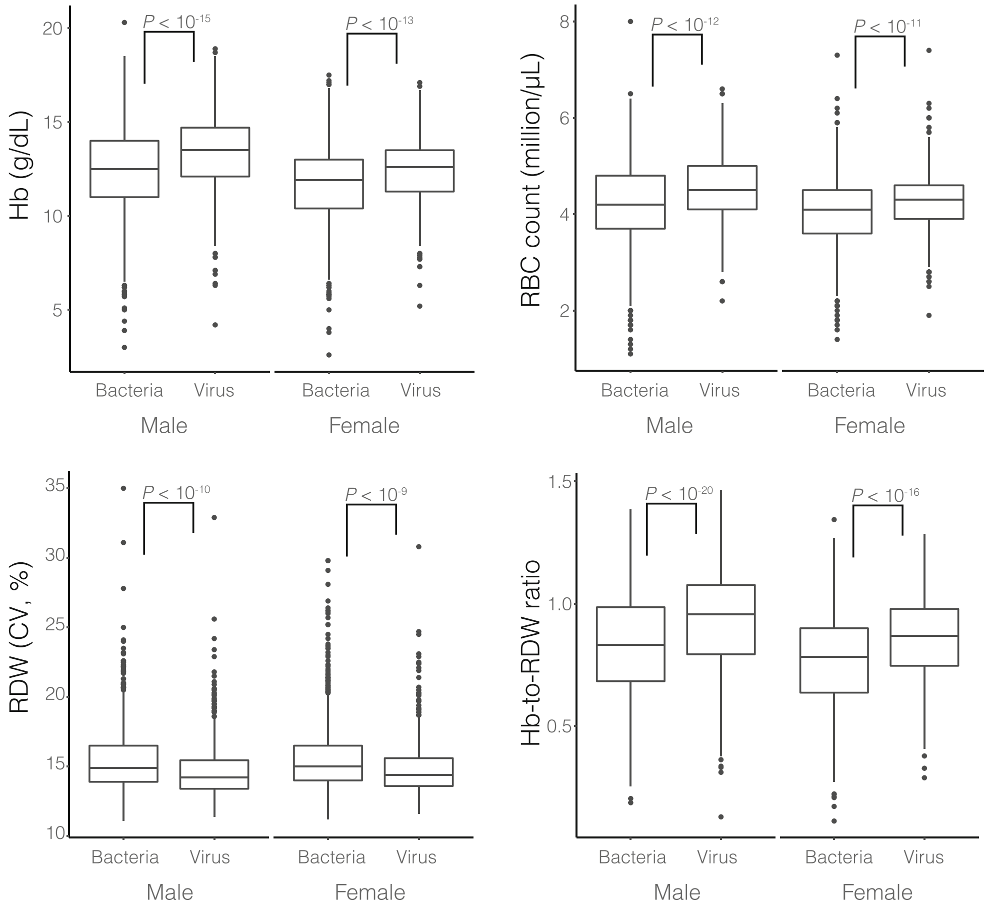

Fig. 2 Significant difference in anemia measurements between viral- and bacterial-infected patients. Boxplots are shown for selected indicators of infection type and gender. *F* test *P* values are presented. Hb, hemoglobin; RBC, red blood cells; RDW, red cell distribution width

48 h.p.a.). Low hazard ratio (HR) corresponded to a longer LOS and a higher HR to a shorter LOS. In general, except for RDW, the majority of anemia measurements were associated with LOS, and all high levels with a shorter LOS (Table 4).

Discussion

In this retrospective study, we investigated the use of anemia-related measurements as biomarkers to distinguish viral from bacterial infections. To the best of our knowledge, this is the first study to examine the importance of these biomarkers for this indication in adult patients. Focusing on adults, we found that more than half of the patients are characterized by low Hb levels upon ED admission, and there exists a strong negative correlation between Hb and RDW measurements. The combination of these markers can be further used to distinguish between viral and bacterial infections, even in patients with relatively low CRP (< 21 mg/L). We further followed the kinetics of anemia-related measurements up to 72 h.p.a. and found that the difference between these two groups of patients was consistent throughout the time period. Moreover, we have shown that most of these markers have an effect on LOS. The ability to use routinely available markers from a complete blood count in order to be able to distinguish between virally and bacterially infected patients is of extremely important, with our findings having possible wider clinical implications.

Previous papers have focused on assessing the association of various anemia-related measurements with disease severity in patients with acute infection or sepsis. Anemia is prevalent in critically ill patients including patients with sepsis [15–18]. A reduction in Hb levels can be an expression of chronic anemia or response to inflammation as well as a combination of both. There are several mechanisms that might contribute to this reduction, including impaired iron metabolism and stress-induced gastro-internal bleeding. Inflammatory cytokine, such as interleukin-1, interleukin-6, interferon gamma, and tumor necrosis factor, could also decrease erythropoietin production and play a key role in the production and survival of RBCs. The combination of these mechanisms could lead to an increase in the morphological variation of RBC size, namely RDW. RDW has previously been shown to predict mortality in critically ill and septic patients [19–22], and has also been described as a prognostic marker for pulmonary hypertension, coronary artery disease, congestive heart failure, etc. [23].

The decrease in Hb levels during the first days following hospitalization of septic patients has been previously reported [16], although the increase in patients with a bacterial

Table 2 Comparison of anemia-related lab tests between virally and bacterially infected patients

		1238 viral patients mean (range)	2645 bacterial patients mean (range)	*P* value, *F* test
Hb (g/dL)	All	12. 9 (4.2–18.9)	12.01 (2.6–20.3)	6.68E-30
	Male	13.35 (4.2–18.9)	12.4 (3.9–20.3)	1.11E-16
	Female	12.39 (5.2–17.1)	11.65 (2.6–17.5)	1.17E-14
Hematocrit (%)	All	38.89 (15–59)	36.53 (10–62)	4.65E-25
	Male	40.08 (15–59)	37.56 (12–62)	5.76E-14
	Female	37.6 (16–52)	35.58 (10–54)	1.72E-12
RBC count (million/μL)	All	4.39 (1.9–7.4)	4.10 (1.1–8)	9.68E-25
	Male	4.5 (2.2–6.6)	4.19 (1.1–8)	1.08E-13
	Female	4.26 (1.9–7.4)	4.02 (1.4–7.3)	1.91E-12
RDW (CV, %)	All	14.77 (11.4–32.9)	15.47 (11.1–35)	1.76E-19
	Male	14.67 (11.4–32.9)	15.37 (11.1–35)	6.56E-11
	Female	14.87 (11.6–30.8)	15.57 (11.2–29.8)	5.21E-10
MCHC (g/dL of RBC)	All	33.21 (22.2–38.2)	32.94 (25.8–73.4)	4.29E-05
	Male	33.33 (22.2–37.6)	33.06 (27.2–73.4)	9.05E-03
	Female	33.07 (26.4–38.2)	32.81 (25.8–47.2)	1.43E-03
MCV (fL)	All	88.95 (56.9–113.6)	89.38 (52.4–143.9)	0.24
	Male	89.39 (58.1–113.6)	89.93 (57.2–143.9)	0.32
	Female	88.45 (56.9–111.8)	88.86 (52.4–125.1)	0.15
MCH (pg/RBC)	All	29.55(15.9–39.2)	29.46 (14.2–80.6)	0.47
	Male	29.81 (15.9–39.2)	29.76 (17.9–80.6)	0.75
	Female	29.26 (18–37.9)	29.18 (14.2–55.5)	0.49
Hb-to-RDW ratio	All	0.89 (0.13–1.47)	0.8 (0.11–1.39)	1.17E-36
	Male	0.93 (0.13–1.47)	0.83 (0.19–1.39)	9.28E-21
	Female	0.85 (0.29–1.29)	0.77 (0.11–1.34)	2.05E-17
CRP (mg/L)	All	63.84 (0–526.7)	65.12 (0–526.7)	1.83E-32
	Male	64.98 (0.1–399.78)	103.15 (0.02–612.52)	2.70E-15
	Female	62.56 (0–526.7)	108.62 (0.03–548.38)	5.48E-19

infection, as opposed to those with a viral infection, has not been described. While this finding may relate to effective antibiotic treatment, the clinical response of these patients needs to be investigated further.

Hb and RDW were first combined as a novel prognostic index to assess their significance in esophageal squamous cell carcinoma patients [24]. Sun et al. revealed a significant association between the Hb-to-RDW ratio and survival outcome. A low Hb-to-RDW ratio was found to be indicative for tumor aggressiveness and advanced-stage tumor. In our study, we found that this ratio was also associated with LOS and that patients with bacterial infection tended to have a lower Hb-to-RDW ratio than virally infected patients. Since calculating this ratio is rather simple, it can be used as an additional biomarker to discern between virally and bacterially infected patients at no additional cost.

Iron deficiency can also be the cause of anemia. Ferritin levels have long been known to be acute-phase reactants [25]; however, other iron measurements, such as serum iron levels and transferrin saturation, have been studied far less. During bacterial infection, the host and the pathogen compete for iron which may lead to iron deficiency and anemia. Though this system has been studied for many years, the difference in iron measurements between virally and bacterially infected patients was never examined in depth. Only one paper [26] studied this association in pediatrics, suggesting that iron and ferritin can be used to distinguish between patients with a viral and bacterial infection. These findings suggest that serum iron measurements may be beneficial in patients presenting with an infectious disease, irrespective of the presence of anemia.

Our study has several limitations: first, it is a one-cohort retrospective study, and the association of our results to different therapies, for example antibiotics, or chronic diseases, which might affect anemia levels, were not investigated due to incomplete data. Second, our cohort included only patients who were referred for comprehensive lab tests (PCR, immunoglobulin, or blood culture) and therefore our results might be affected by selection bias. Third, we based our analysis on lab tests taken up to72 h.p.a., while disease onset was unknown. Fourth, our initial cohort included a group of 163

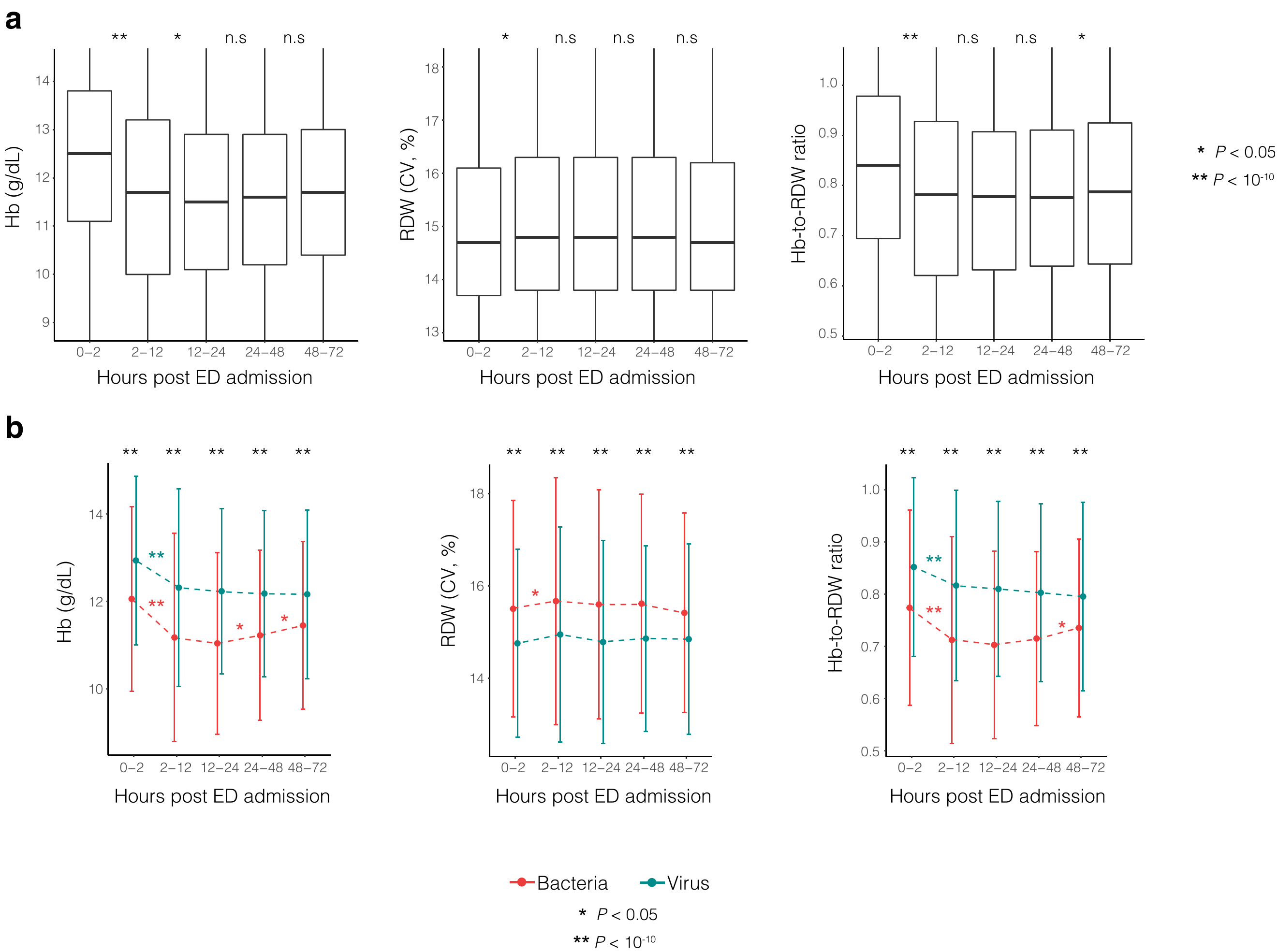

Fig. 3 Changes in anemia measurements over time post ED admission. **a** Boxplots of consecutive measurements of Hb (left), RDW (middle), and Hb-to-RDW (right) up to 72 h post ED admission are shown for all individuals, regardless of infection type. The observations were divided into 5 groups by time. *P* value for the difference in the distribution of measurements between consecutive time points is depicted. **b** As in **a**, but divided into patients infected by either a virus (green) or bacteria (red). *P* value for the *F* test at each time point between those infected by a virus or bacteria is presented in black on top. *P* value for the difference in the distribution of measurements between consecutive time points is depicted for each group of patients separately, using the same color code. ED, emergency department

patients who were co-infected with viral and bacterial agents. Despite the importance of this group, we decided to exclude it due to its size (less than 5% percent of our cohort) and ambiguity in the disease origin. This group should be further explored in a larger cohort. Fifth, approximately one-third of our cohort included patients under the age of 65, and although we found a significant association of Hb-to-RDW in both sub-populations, further studies including a broader set of patients

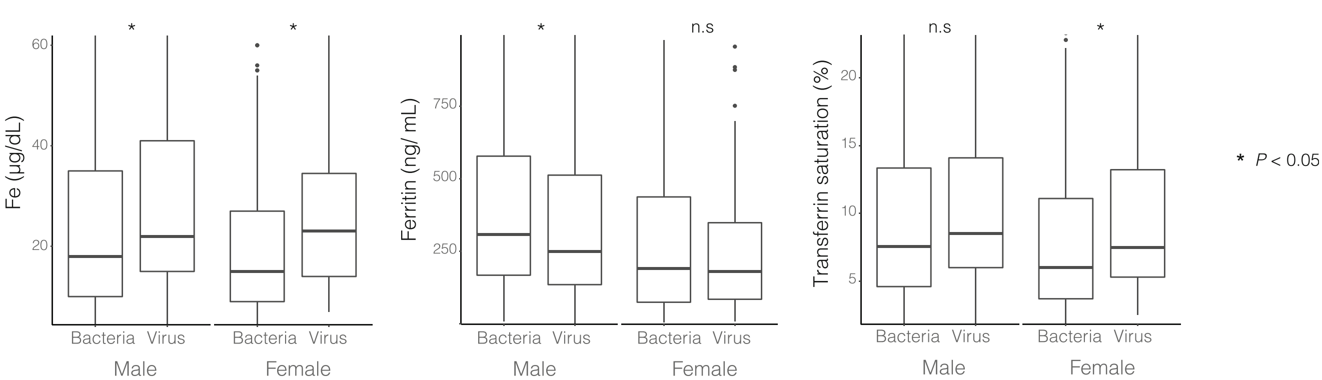

Fig. 4 Iron measurements taken between 12 and 48 h post ED admission. Boxplots of Fe (left), ferritin (middle), and transferrin saturation (right) by infection and gender. ED, emergency department

Table 3 Comparison of iron and ferritin-related lab tests between virally and bacterially infected patients

		194 viral patients mean (range)	424 bacterial patients mean (range)	*P* value, *F* test
Fe (μg/dL)	All	32.79 (3–439)	26.78 (2–248)	2.37E-4
	Male	35.97 (3–439)	28.83 (3–233)	0.03
	Female	28.40 (7–230)	24.83 (2–248)	1.9E-3
Ferritin (ng/mL)	All	327.27 (1.8–1573)	404.83 (5.4–5500.2)	0.01
	Male	360.57 (1.8–1505.9)	463.99 (9.3–5500.2)	8.79E-3
	Female	281.37 (8.5–1573)	348.92 (5.4–1649.9)	0.44
Transferrin saturation (%)	All	11.21 (0.9–95)	10.77 (0.6–82.1)	0.07
	Male	12.19 (0.9–95)	12.04 (1.3–82.1)	0.58
	Female	9.86 (2.5–36.5)	9.55 (0.6–81.1)	0.03
Hb (g/dL)	All	11.72 (3.7–17.2)	10.56 (3.6–17.3)	9.78E-10
	Male	12.08 (2.7–17.2)	10.79 (3.6–17.3)	2.63E-6
	Female	11.24 (6.9–15.7)	10.35 (5.8–15.8)	1.04E-4
Hematocrit (%)	All	35.36 (13–50)	32.15 (11–54)	1.05E-8
	Male	36.27 (13–50)	32.86 (11–54)	2.61E-5
	Female	34.14 (22–49)	31.51 (18–50)	1.1E-3
RBC count (million/μL)	All	4.03 (2.3–6.1)	3.65 (1.4–5.9)	4.06E-9
	Male	4.10 (2.3–6.1)	3.68 (1.4–5.8)	1.03E-5
	Female	3.95 (2.5–6.1)	3.62 (1.8–5.9)	1.14E-4
RDW (CV, %)	All	15.37 (12.1–33.4)	15.86 (11.9–27)	0.01
	Male	15.25 (12.1–33.4)	15.85 (11.9–23.5)	7.17E-3
	Female	15.53 (12.7–22.8)	15.87 (12.1–27)	0.48
MCHC (g/DL of RBC)	All	33.21 (27.8–52.1)	32.92 (28.3–38.7)	0.02
	Male	33.37 (27.8–52.1)	32.9 (28.3–38.7)	0.01
	Female	33.01 (29.3–37.3)	32.93 (29.6–36.3)	0.8
MCV (fL)	All	87.91 (58.4–112.8)	88.44 (61.5–118.7)	0.56
	Male	88.78 (58.4–110.1)	89.53 (61.5–118.5)	0.53
	Female	86.75 (62–112.8)	87.47 (64.6–118.7)	0.89
MCH (pg/RBC)	All	29.26 (16.2–57.4)	29.17 (18–41.8)	0.73
	Male	29.72 (16.2–57.4)	29.53 (18–40.3)	0.59
	Female	28.66 (18.2–36.1)	28.85 (20–41.8)	0.91
Hb-to-RDW	All	0.79 (0.11–1.34)	0.68 (0.25–1.17)	2.05E-8
	Male	0.82 (0.11–1.34)	0.7 (0.25–1.12)	2.24E-6
	Female	0.74 (0.36–1.12)	0.67 (0.25–1.17)	2.02E-3
CRP (mg/L)	All	88.56 (0.39–443.25)	130.04 (0.12–405.84)	1.87E-6
	Male	89.14 (0.66–443.25)	123.27 (0.12–371.98)	1.73E-4
	Female	87.79 (0.39–402.5)	136.27 (0.18–405.84)	3.09E-3

are needed to validate our results and to investigate the effect of antibiotic treatment and disease onset. Last, our results do not provide recommendation for clinical use and further studies will be needed in order to introduce our findings into the clinical setting.

Table 4 Multivariate Cox regression model length of hospital stay

Parameter	HR (95% CI)	*P* value
Fe (μg/dL)	1 (0.998–1.002)	ns
Ferritin (ng/mL)	0.99 (0.9997–1.00)	0.007
Transferrin saturation (%)	0.993 (0.987–1.00)	0.008
Hb (g/dL)	1.08 (1.06–1.1)	$P < 10^{-16}$
Hematocrit (%)	1.022 (1.017–1.028)	$P < 10^{-13}$
RBC count (million/μL)	1.18 (1.12–1.23)	$P < 10^{-10}$
RDW (CV, %)	0.91 (0.89–0.92)	$P < 10^{-16}$
MCHC (g/dL of RBC)	1.07 (1.05–1.1)	$P < 10^{-16}$
MCV (fL)	1.003 (0.998–1.01)	ns
MCH (pg/RBC)	1.02 (1.01–1.03)	$P < 10^{-4}$
Hb-to-RDW ratio	3.15 (2.61–3.79)	$P < 10^{-16}$
CRP (mg/L)	0.99 (0.998–0.999)	$P < 10^{-5}$

The different anemia measurements used in our study are cost-effective and can be used in conjunction with other laboratory markers to assist in differentiating between bacterial and viral infection during the first 24 h.p.a.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethical approval and inform consent The study was reviewed and approved by the Tel-Aviv medical center institutional Helsinki Committee (number 0491-17). Study participants gave their written informed consent for participation according to the instructions of the local ethics committee.

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