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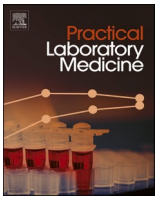

# Validation of a whole blood machine learning strategy for distinguishing between bacterial and viral infection in a pediatric hospital setting

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ABSTRACT

Similar symptoms between viral and bacterial diseases often make diagnosis difficult. This study assessed the clinical performance of the newly cleared whole-blood Bacterial versus Viral Score assay in our pediatric cohort to the previously validated serum assay and emergency department physician diagnosis. This assay shows excellent agreement (R = 0.997) with the serum assay and has great diagnostic accuracy when compared to physician diagnosis.

## 1. Introduction

Many pediatric ED visits in the US are mostly due to infectious diseases which can either be viral, bacterial, or co-infections or other sources [1,2]. Due to the difficulties in distinguishing viral from bacterial infections in pediatric clinical settings because of symptom overlap, physicians often prescribe antibiotics empirically out of concern over the sequelae of bacterial infection [1,3]. Studies have reported different inappropriate antibiotic prescriptions in children [4–7]. This inappropriate use of antibiotics drives antibiotic resistance which has been referred to as one of the greatest threats to public health by the CDC [8,9]. A diagnostic test that can help discriminate infection etiology early could be beneficial to ED physicians and assist them in prescribing antibiotics appropriately.

The Bacterial versus Viral (BV) Score assay is a multivariate index test that measures and computationally integrates the concentration of three host-immune proteins- TNF-related apoptosis-inducing ligand (TRAIL), C-reactive protein (CRP), and interferon-gamma inducible protein-10 (IP-10) into a BV Score (0-100) to aid in differentiating between viral and bacterial infections [1, 10–12]. We validated the first FDA-cleared serum-based BV ($S_r$-BV) Score assay in our pediatric population and showed that it has excellent precision, great diagnostic accuracy, and is not affected by the two most common interferences in pediatric specimens [1]. Recently, the FDA cleared the whole-blood BV (WB-BV) Score assay which has the advantage of a faster resulting time by eliminating the steps for serum isolation while retaining the performance of its serum counterpart. Given these potential advantages, and its small volume requirement which makes it ideal in a pediatric setting, we conducted a study to compare the performance of the WB-BV Score assay to the established $S_r$-BV Score assay in our pediatric cohort.

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**List of abbreviations**

| | |
|---|---|
| ED | Emergency department |
| BV | Bacterial versus Viral |
| $S_r$-BV | Serum-based Bacterial versus Viral |
| WB-BV | Whole-blood Bacterial versus Viral |

## 2. Materials and methods

A retrospective cohort study was conducted using whole blood and paired serum samples from twenty (20) pediatric patients with acute febrile illness who visited the emergency department of the Texas Children's Hospital, Houston, TX. The criteria for inclusion and exclusion were the same as in our previous study [1]. Samples were tested on the MeMed Key analyzer. For clinical validation, we compared the WB-BV Score test results with both microbiological confirmation by either blood cultures or PCR and physician diagnosis. The correlation between the WB-BV Score and $S_r$-BV Score assays was compared using Pearson's correlation coefficient. Deming regression and Bland-Altman plots were generated using EP Evaluator 12.0 software.

## 3. Result

### 3.1. Demographic and clinical diagnosis

Table 1 shows the demographic and clinical diagnosis made by ED physicians based on clinical and microbiological or radiological evidence. Of the 20 patients, 10 were diagnosed with viral infection, 8 with bacterial infection, and 2 with viral and a high likelihood of bacterial co-infection. Both BV Score tests classified 11 samples as viral, 7 as bacterial, and 2 with an equivocal outcome.

### 3.2. Similar correlation between both whole blood and serum BVS assays

The WB- BV Score assay was 100% in agreement with the $S_r$- BV Score assay in classifying patients as either having viral or bacterial infections (Table 2). Both assays classified our 20 patient cohorts as 55% viral, 35% bacterial, and 10% equivocal comparable to 50% viral, 40% bacterial and 10% co-infection diagnosis by ED physicians (Table 2).

Our method comparison data reveal that the WB-BV Score test shows excellent agreement with our previously validated serum test. The Deming regression for the assay score yielded a slope of 0.976 and an intercept of 1.7 (Fig. 1). The calculated bias was 0.7% with a Pearson's correlation coefficient (R) of 0.997 (Fig. 1).

## 4. Discussion

One of the major issues in pediatric laboratory testing is the small blood volumes in pediatric patients, thus an assay that requires whole blood specimens is preferred for pediatric laboratory testing [13]. The correlation between the WB- BV Score and $S_r$-BV Score assays was carried out to assess its performance in our laboratory. Our results are consistent with our previous studies on the serum matrix [1]. Given that the assay takes 15 min per run, we anticipate a rapid turnaround time of 20-30 min which is faster than the earlier 1 h for our serum-based test. As most patients who visit our emergency department usually have blood drawn for a complete blood count, the need for additional blood drawn for serum isolation is eliminated as the initial blood drawn can be used to run the assay. This present study shows that the multivariate WB-BV Score assay is also clinically useful in classifying pediatrics with febrile illness with unknown origin as either viral or bacterial infection.

**Table 1**
Demographics and clinical diagnosis of study pediatric cohort by ED physicians.

| CHARACTERISTIC | TOTAL PATIENTS (N = 20) |
|---|---|
| **AGE (YEARS)** | 0.2-18 |
| **GENDER** | |
| **MALES** | 11 |
| **FEMALES** | 9 |
| **ANTIBIOTIC PRESCRIPTION (%)** | 13 |
| **DIAGNOSIS** | |
| **VIRAL** | 10 |
| **BACTERIAL** | 8 |
| **CO-INFECTION** | 2 |

**Table 2**
Patient disease classification using both the serum and whole blood BVS assay in comparison to ED physicians' diagnosis.

| Disease classification | | | ED physician diagnosis (%) |
|---|---|---|---|
| | Serum (%) | Whole Blood (%) | |
| **Viral** | 11 (55) | 11 (55) | 10 (50) |
| **Bacterial** | 7 (35) | 7 (35) | 8 (40) |
| **Equivocal** | 2 (10) | 2 (10) | 2 (10) |
| **Total** | 20 (100) | 20 (100) | 20 (100) |

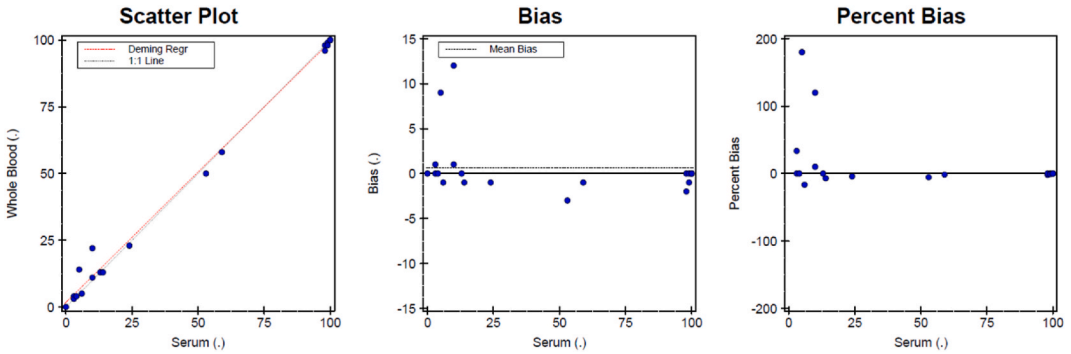


**Fig. 1.** WB-BV Score test correlates well with the serum BV Score test. Bland-Altman analysis for method comparison using blood and serum samples (n = 20). Scatter plot (A) shows the Deming regression, bias plot (B), and percent bias plot (C). The correlation equation is given by y = 0.976x +1.7, with bias = 0.7% and R = 0.997.

## CRediT authorship contribution statement

**Ridwan B. Ibrahim:** Data curation, Methodology, Validation, Writing – original draft. **Herda Ona:** Formal analysis. **Anil K. Chokkalla:** Resources, Writing – original draft, Writing – review & editing. **Estella Tam:** Resources. **Sridevi Devaraj:** Conceptualization, Investigation, Project administration, Writing – original draft, Writing – review & editing.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

Data will be made available on request.

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