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The Role of Widal, Typhidot and Tubex-TF Examinations in The Diagnosis of Typhoid Fever

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Abstract.
Typhoid fever is a systemic infection caused by Salmonella enterica serovar Typhi and Paratyphi. The disease is transmitted through contaminated food or water and is endemic in many developing countries, including Indonesia. Timely and accurate diagnosis is essential for the management of this disease. Serological tests, such as Widal, Typhidot, and Tubex-TF tests, are the main methods for the diagnosis of typhoid fever. Each test has its advantages and disadvantages in terms of sensitivity, specificity, and ease of use. The Widal test, although widely used, often cross-reacts with other bacterial infections and has varying sensitivities. Typhidot offers faster detection with high accuracy in the early stages of infection but is still susceptible to cross-reaction. Meanwhile, Tubex-TF uses a semi-quantitative method that can provide results quickly, although the interpretation of results may vary depending on the user's skills. The selection of these serological test methods needs to be adjusted according to clinical factors, laboratory facilities, and resource availability. This study aims to compare the diagnostic performance of the three serological tests in the context of typhoid fever diagnosis in developing countries through a systematic literature review. The results of the analysis showed that Typhidot had the highest negative predictive value (100%), while Tubex-TF showed better sensitivity (76%) and specificity than Widal. The conclusion of this study can serve as a consideration for clinicians and laboratory personnel in choosing the diagnostic test most suitable for local conditions.
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Keywords: Typhoid fever, Salmonella enterica, Widal test, Typhidot, Tubex-TF, Serological diagnosis, Systemic infection.

INTRODUCTION

Typhoid fever, also known as enteric fever, is a multisystemic disease characterized by abdominal pain and fever. It is caused by *Salmonella Typhi* (or *Salmonella Paratyphi* A, B, and C). *Typhoid* and *paratyphoid fever* are clinically indistinguishable. *Typhoid fever* is a leading cause of community-acquired bloodstream infection in South and Southeast Asia (WHO, 2023).

In Indonesia, this disease is endemic and a public health problem. Case studies in major hospitals in Indonesia show a year-on-year increase in *typhoid* cases, with a morbidity rate of 500 cases per 100,000 population and an average mortality rate of 0.6–5% (Asadi et al., 2022; Casman et al., 2023; Efendi et al., 2022; Jagadishkumar et al., 2016; Khalid et al., 2022; Nelwan et al., 2023). The incidence of *typhoid fever* is higher in populations with a lack of clean water and inadequate sanitation. Children are at greater risk of developing *typhoid fever* (WHO, 2023).

A definitive diagnosis of *typhoid fever* is achieved by isolating *S. typhi* or *S. paratyphi* from a positive blood sample. However, culture testing has several limitations: adequate facilities and skilled personnel are required; the test is relatively expensive; and it takes a long time, while clinicians require faster results (Sapkota et al., 2023). A negative culture result does

not rule out *typhoid fever* because identification of the bacteria from various specimens is influenced by the timing of specimen collection, antibiotic administration before culture, and insufficient blood volume. Various serological tests for *typhoid* are currently available, such as the *Widal* test, *Tubex-TF* test, and *Typhidot* test, each with varying accuracy.

In response to the limitations of culture, serological tests such as the *Widal* test, *Typhidot*, and *Tubex-TF* have been developed and widely adopted, especially in developing countries. Previous studies have evaluated these tests individually, often reporting varied performance metrics. For instance, the *Widal* test is notorious for cross-reactivity and low specificity, while *Typhidot* offers rapid results but may still yield false positives. *Tubex-TF* shows promise with good sensitivity but suffers from subjective interpretation (Khanna et al., 2015). However, many existing studies focus on a single test or compare only two tests, and there is a lack of comprehensive, comparative analyses that simultaneously evaluate all three against a common standard in a high-burden setting. Moreover, the applicability of findings from one region may not translate directly to others due to differences in endemicity, population immunity, and circulating strains.

This study aims to fill this gap by providing a contemporary, systematic comparison of the diagnostic accuracy (sensitivity, specificity, predictive values) of the *Widal* test, *Typhidot*, and *Tubex-TF* in an Indonesian context. The novelty lies in its direct, head-to-head comparison of all three rapid serological tests against blood culture, assessing their practical utility, operational challenges, and cost-effectiveness within the constraints of a developing country's healthcare system.

This literature review aims to discuss the role of these three serological tests in diagnosing *typhoid fever*. The benefits of this research are multifold. It will provide clinicians and laboratory personnel with clear, practical guidance for choosing the most appropriate diagnostic tool, ultimately leading to more accurate diagnoses, timely treatment, better patient outcomes, and optimized use of limited healthcare resources. Furthermore, the findings will contribute valuable local data to the global discourse on *typhoid fever* diagnostics and inform public health strategies aimed at controlling this endemic disease.

METHOD

Participants included individuals clinically suspected of having typhoid fever, as well as control groups such as healthy individuals and patients diagnosed with other conditions like malaria, respiratory infections, or urinary tract infections.

The testing procedures involved:

- The Widal test, using slide and tube agglutination methods to detect antibodies (O and H) against *Salmonella Typhi* and *Paratyphi*.
- The Typhidot test, an immunochromatographic assay detecting IgM and IgG antibodies against *Salmonella Typhi*, conducted on serum, plasma, or whole blood samples.
- The Tubex-TF test, a semi-quantitative assay detecting IgM antibodies against *Salmonella Typhi* O9 via Inhibition Magnetic Binding Immunoassay (IMBI).

For analysis, results from the three tests were compared with blood culture as the gold standard. Sensitivity, specificity, positive and negative predictive values, and kappa statistics were calculated. Statistical analyses assessed the reliability of these tests in different clinical settings, addressing issues like cross-reactivity and false positives.

RESULTS AND DISCUSSION

Definition

Typhoid fever, also known as enteric fever, is a systemic disease caused by Salmonella enterica serovar typhi (S. Typhi) or Salmonella paratyphi (S. Paratyphi) A, B, and C (WHO, 2023).

Epidemiology

The high incidence of typhoid fever is associated with poor sanitation and lack of access to clean drinking water. In endemic areas, typhoid fever is more common in urban areas than in rural areas and is more common among children and adolescents. Risk factors for this disease include drinking or eating contaminated food, raw fruits and vegetables, poor handwashing, and Helicobacter pylori infection (a condition that causes decreased stomach acid), all of which contribute to the development of typhoid fever.

Etiology

Typhoid fever is caused by Salmonella Typhi or Salmonella Paratyphi. Salmonella belongs to the Enterobacteriaceae family. Salmonella are medium-sized (0.3 to 1.0 × 1.0 to 6.0 μm), non-spore-forming, Gram-negative rods that possess a common antigen (enterobacterial common antigen). All members can grow rapidly, both aerobically and anaerobically (Murray, Rosenthal & Pfaller. 2021)

Salmonella Structure

Enterobacteriaceae have a complex antigenic structure. Enterobacteriaceae are classified into more than 150 heat-stable somatic O (lipopolysaccharide) antigens, more than 100 heat-labile K (capsular) antigens, and more than 50 flagellar H (flagellar) antigens. In Salmonella, the capsular antigen is called the Vi antigen.

This disease is transmitted through food or drink contaminated with the bacteria. The primary source of infection is humans who are acutely ill or are asymptomatic carriers.

The O antigen, or somatic O antigen, is the outermost antigenic portion of the lipopolysaccharide cell wall, consisting of repeating polysaccharide units. The O antigen is resistant to boiling, alcohol, and acid. The most abundant antibody against the O antigen is IgM. Each genus of Enterobacteriaceae has a specific O antigen, but an organism can have multiple O antigens. E. coli can cross-react with Providencia, Klebsiella, and Salmonella species. O agglutination is slower and less immunogenic, but it has high diagnostic value. Antibody titers elicited by O antigens are always lower than H antibody titers.

The K antigen or Vi antigen in some Enterobacteriaceae is located on the outside of the O antigen or is a surface antigen and is thermolabile. The K or Vi antigen is associated with the virulence of the bacteria. Antibodies formed against the Vi antigen persist for a long time in the blood and indicate that the individual is a carrier of the bacteria. The Vi antigen is found in S. typhi, S. paratyhpi C, and S. Dublin.

The H antigen, or flagellar antigen, is located on the flagella and can be denatured by boiling or alcohol. The H antigen is a thermolabile and highly immunogenic protein. Anti-H

antibodies are usually IgG. The antigenicity of the H antigen is determined by the amino acid composition of the flagellar protein (flagellin). Within a single serotype, the flagellar antigen can exist in two forms, phase 1 and phase 2. Organisms typically tend to shift from one phase to the other, a phenomenon known as phase variation. The H antigen on the bacterial surface can interfere with agglutination by anti-O antibodies.

Pathogenesis of Typhoid Fever

S. Typhi and S. Paratyphi bacteria enter the human body through contaminated food. Some bacteria are destroyed in the stomach, while others pass into the intestines and continue to multiply. Salmonella bacteria can escape the stomach because they are resistant to stomach acid pH as low as 1.5. If the intestinal mucosal humoral immune response (IgA) is inadequate, the bacteria will penetrate epithelial cells (especially M cells) and then into the lamina propria. Furthermore, some pathogenic Salmonella species are phagocytosed by phagocytic cells. These cells then pass through the mucosa and present the bacteria to macrophages in the lamina propria. In the lamina propria, the bacteria multiply and are phagocytosed by phagocytic cells, primarily macrophages. The bacteria can survive and reproduce within cells and are therefore protected from the immune system.

The bacteria are then carried to the Peyer's patches of the distal ileum and then to the mesenteric lymph nodes. Then, through the thoracic duct, the bacteria contained within these macrophages enter the bloodstream (resulting in asymptomatic initial bacteremia) and spread throughout the body's reticuloendothelial organs, especially the liver and spleen. In these organs, they continue to multiply until they reach a critical level. The bacteria then induce macrophage apoptosis, leaving the phagocytic cells and multiplying outside the cells or sinusoidal spaces. They then re-enter the bloodstream, resulting in a second bacteremia accompanied by signs and symptoms of systemic infection.

In the liver, the bacteria enter the gallbladder, multiply, and are excreted intermittently along with bile into the intestinal lumen. Some of the bacteria are excreted in the feces, while others re-enter the circulation after penetrating the intestine. The same process repeats itself, as macrophages are activated and hyperactive, leading to the release of inflammatory mediators during phagocytosis of Salmonella bacteria, which subsequently lead to systemic inflammatory reactions such as fever, malaise, myalgia, headache, abdominal pain, vascular instability, mental disturbances, and coagulation. In Peyer's plaques, hyperactive macrophages induce tissue hyperplasia (S. Typhi intramacrophages induce delayed-type hypersensitivity reactions, tissue hyperplasia, and organ necrosis). Gastrointestinal bleeding can occur due to erosion of blood vessels around Peyer's plaques that undergo necrosis and hyperplasia due to the accumulation of mononuclear cells in the intestinal wall. This pathological process in lymphoid tissue can progress to the muscle layer and intestinal serosa, and can result in perforation. Endotoxins can attach to capillary endothelial cell receptors, resulting in complications such as neuropsychiatric, cardiovascular, respiratory, and other organ disorders (Hartanto, 2021; Khairunnisa et al., 2020; Mustofa et al., 2020; Saputra, 2021; Widyawati et al., 2022).

Diagnosis of Typhoid Fever

The diagnosis of typhoid fever must take into account the patient's travel history to areas where typhoid is endemic. The clinical manifestations of typhoid fever are nonspecific. Several

diseases have similar symptoms, including malaria, hepatitis, bacterial enteritis, dengue fever, rickettsial infections, leptospirosis, amoebic liver abscess, and HIV infection. Typical symptoms of typhoid fever are fever and abdominal pain. Typhoid can be asymptomatic in carrier patients.

The incubation period for S. Typhi ranges from 10-14 days, depending on the size of the inoculum and the host's health and immune status. Other symptoms may include headache, chills, cough, sweating, and myalgia. Gastrointestinal symptoms include anorexia, nausea, vomiting, and diarrhea, with constipation more common. A physical examination may reveal a dirty tongue, splenomegaly, and abdominal tenderness. Early signs include a rash (rose sign 30%), hepatosplenomegaly, epistaxis, and relative bradycardia at the peak of a high fever (<50%).

Laboratory hematology tests can reveal leukopenia and neutropenia in 15-25% of cases. Leukocytosis is more common in children during the first 10 days of illness and in cases complicated by perforation or secondary infection. Other laboratory tests are nonspecific, such as elevated liver function tests and muscle enzyme levels.

The gold standard for typhoid fever is culture, which involves isolating S. Typhi or S. Paratyphi from blood, bone marrow, other sterile sites, stool, or gastrointestinal secretions. Culture sensitivity is 40-80%, this is likely due to the frequent use of antibiotics in endemic areas and the low number of S. Typhi (i.e. <15 organisms/mL) present in the blood.

Serologic Testing For Typhioid Fever

Serological tests based on antibody detection using the Widal, Typhidot, and TUBEX-TF tests are currently the standard serological tests. Various studies have developed faster, more sensitive, and more specific serological tests, such as the TUBEX-TF or Typhidot, which can be used to diagnose typhoid fever. However, serological tests have varying sensitivity and specificity values.

1) WIDAL

The Widal test is a serological test based on the principle of agglutination to aid in the diagnosis of enteric fever (typhoid fever or paratyphoid fever). This test is named after its inventor, Georges Fernand Isidore Widal, a French physician and bacteriologist. There are two methods of agglutination testing: using a tube and using a slide (Dahal P., 2022).

2) Test Principle:

The principle of the Widal test is the antigen-antibody agglutination reaction. This test aims to detect antibodies in the patient's serum against the O (somatic) and H (flagellar) antigens of Salmonella Typhi and Paratyhpi A, B, and C. The Widal test uses bacterial suspensions of S. Typhi and S. Paratyphi, using dead and stained O and H antigens. If the patient's serum contains antibodies that react with the antigens contained in the Widal reagent, an agglutination reaction will occur which is interpreted as a positive Widal. If you want to know the titer, a re-examination is carried out by diluting the serum. The result reported is the highest dilution that produces a positive result (Dahal 2022). Somatic O IgM antibodies can be detected 6-8 days after infection and represent the initial serological response in early typhoid fever, while IgG flagella H antibodies can be detected on days 10-

12 but last longer. The Widal test result is considered positive if the O agglutinin titer is at least 1/320 or there is a 4-fold increase in titer on repeat examination with an interval of 5-7 days (Ministry of Health 2022).

3) Limitations of the Widal Test

A positive Widal result can occur in patients with typhoid fever, but it can also be due to a history of immunization with Salmonella antigens, the similarity of O and H antigens, which can lead to cross-reactions with non-typhoidal Salmonella or other Enterobacteriaceae, or cross-reactions with infections with non-Salmonella organisms (malaria, dengue, miliary tuberculosis, endocarditis, chronic liver disease, brucellosis).

A negative Widal result does not always mean the patient is not infected with S. typhi. It can be caused by the patient being a carrier, an insufficient inoculum of bacterial antigen in the host to induce antibody production, technical difficulties or errors in the test, the administration of antibiotics prior to the test, or variations in antigen preparation.

4) TYPHIDOT

Typhidot is a qualitative immunochromatographic test that detects IgM and IgG antibodies against specific Salmonella bacteria found in serum, plasma, or whole blood. This test detects IgM and IgG antibodies against The outer membrane protein (OMP) of Salmonella typhi. Typhidot becomes positive on days 2-3 of infection and can detect IgM and IgG separately.

5) Test Principle

The Typhidot Rapid IgM test is an immunochromatographic test using an indirect solid phase. This test is based on the presence of a specific S. Typhi antigen in the form of 50Kd OMP immobilized on a layer of cellulose nitrate. Typhidot is also easy to perform and does not require special equipment. Currently, two types of Typhidot tests have been released: one that detects only IgM and one that detects both IgM and IgG. The interpretation of the results is as follows: if both IgM and IgG are positive, or only IgM is positive, the patient has acute typhoid fever. If only IgG is positive, the patient has had a typhoid infection. If both IgM and IgG are negative, the patient does not have a typhoid infection.

6) Limitations of Typhidot

The Typhidot kit is designed for use only on serum, plasma, and whole blood samples. This test is a qualitative assay and cannot determine antibody levels or concentrations. The intensity of the color in the line does not correlate with the antibody titer in the specimen. Test results must be interpreted in conjunction with other test results and the patient's clinical information. False-positive results may occur.

7) TUBEX-TF

Tubex-TF is a test to help diagnose the acute phase of typhoid fever by detecting immunoglobulin M (IgM) against Salmonella Typhi O9 lipopolysaccharide in patient serum. TUBEX-TF uses a new technology called Inhibition Magnetic Binding

Immunoassay (IMBI), a semi-quantitative colorimetric test with a 10-minute test time.

8) TUBEX-TF Test Principle

IMBI-Inhibition Magnetic Binding Immunoassay is based on visual interpretation of the color change in the liquid resulting from the reaction between the sample and reagent. This test is capable of detecting IgM anti-Salmonella Typhi O9 antibodies in patient serum. Antibodies present in the serum inhibit the reaction between antigens coated with magnetic particles and antibodies coated with colored latex particles. The resulting color is proportional to the concentration of IgM anti-Salmonella Typhi O9 antibodies in the patient's serum. Test results are scored based on visual interpretation, with a score of 0–2 considered negative, a score of 3 considered borderline (inconclusive) and therefore requiring repeat testing, a score of 4 considered weakly positive, and a score of 6–10 considered strongly positive.

9) Limitations of Tubex-TF

Test results with Tubex-TF can be influenced by several factors, including inappropriate reagent or sample amounts due to pipetting errors, inhomogeneous particle suspensions caused by inadequate shaking, the use of the wrong anticoagulant (heparin should be used), icteric or hemolyzed samples, and post-separation reaction interference.

These factors can lead to false-negative results due to too much brown reagent, which can interfere with the binding of the patient's IgM to the kit's IgM. False-positive results caused by too little blue or brown reagent saturate the brown reagent, leaving unbound blue reagent in the supernatant.

10) Performance of Widal, Typidot, and TUBEX-TF

A cross-sectional study conducted at the Dshang Regional Hospital in Cameroon, Central Africa, compared stool culture with two Widal test techniques in patients with clinical typhoid fever. Culture is the gold standard for diagnosing typhoid fever. Blood culture is more sensitive than stool culture, but the advantage of stool culture is that it can be performed throughout the course of the disease. A total of 750 participants participated in the study. The results showed that 325 (43.33%) tested positive for the Widal slide agglutination test, 174 (23.20%) tested positive for the Widal tube titration test, and 159 (21.20%) tested positive for stool culture. The high percentage of Widal slide agglutination tests is likely due to cross-reactions with antibodies from non-bacterial infections such as malaria, dengue fever, and hepatitis, or possibly because the study was conducted in an endemic population. False-negative results in the slide agglutination test can be caused by early typhoid infection, resulting in antibody levels not yet high enough to be detected. The sensitivity of the Widal slide agglutination test and the Widal tube titration test is 97.48% and 100%, respectively. These results (Table 1) demonstrate the Widal test's ability to detect true positive results compared to stool culture (Natheu & Telefo, 2020).

In this study, the Positive Predictive Value for the Widal slide agglutination test was low (47.69%) but very high for the Widal tube titration test (91.37%). The Negative Predictive Value for the Widal slide agglutination test was 99.22% and 100% for the Widal tube titration test. This indicates that a negative Widal test result has good predictive value

for the absence of disease, but a positive result has low predictive value for the presence of typhoid fever, especially in the case of the Widal slide agglutination test (Natheu & Telefo, 2020).

Table 1. Sensitivity, specificity, negative predictive value, positive predictive value, and kappa test of the Widal slide agglutination test and the Widal tube titration test compared with stool culture

Test methods	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Kappa test
Widal slide agglutination test	97.48	71.23	47.69	99.22	0.49
Widal tube titration test	100	97.46	91.37	100	0.94

Description: positive predictive value (PPV); negative predictive value (NPV).

With stool culture, the Widal slide agglutination test had moderate agreement (kappa = 0.47), but the Widal tube titration test had absolute agreement (kappa = 0.94). This indicates that the results obtained from the Widal slide agglutination test in the diagnosis of typhoid fever are less reliable than those obtained from stool culture. Therefore, the Widal slide agglutination test cannot be used alone in the diagnosis of typhoid fever because many patients will be falsely diagnosed positive (Natheu & Telefo, 2020).

Krishna et al., conducted a study of 186 patients with clinically confirmed typhoid in Bangalore, India. Of the 186 patients, 50 (64%) were culture-positive for S. typhi (Group I), with 50 of those tested also positive for Typhidot. Blood cultures also grew other organisms (Group II) - 22 isolates were identified as S. Paratyphi, 4 were identified as S. typhimurium, and 2 were identified as E. coli and all 28 of these patients were Typhidot positive. Blood cultures remained sterile and Typhidot negative in the remaining samples from patients with febrile illness (table 2).

Table 2. Results of Blood Culture and Typhidot Examination

		No. of subjects (n = 186)	Typhidot positive results
Group I	Blood culture with *S.typhi* isolates	50	50
Group II	Blood culture with other than *S. typhi* isolates(including S. paratyphi A)	28	28
Group III	Blood culture negative but clinically typhoid	11	0

Based on the results, Typhidot had a sensitivity of 100% compared to blood culture, a specificity of 95.5%, a positive predictive value (PPV) of 89.2%, and a negative predictive value (NPV) of 100%. However, cross-reactivity with S. paratyphi A (28.2%) was documented and considered unavoidable. Based on this, the results indicate that there is an 89.2% probability of a patient being diagnosed with typhoid fever when tested with Typhidot. The predictive value for a negative test result is calculated as 100%, meaning that if the Typhidot result is negative, there is a 100% probability that the patient does not have

typhoid fever. A study conducted by Bakr evaluating the TUBEX-TF with the Widal test for diagnosing typhoid fever in Kafr El-Shekh, Egypt, found that the TUBEX-TF compared to the Widal test had a sensitivity of 74.6%, specificity of 75%, and accuracy of 75%, while the Widal test had a higher yield. According to the researchers, the TUBEX-TF has a serious drawback related to its scoring system. With this system, a clear result is either a strong positive or a strong negative. In most cases, TUBEX-TF results often fall between a strong positive and a strong negative, and scoring can be performed by different individuals, leading to varying interpretations.

A cross-sectional study in India by Khanna et al. In 2015, samples were taken from 100 healthy participants (group I), 50 samples from patients with a confirmed diagnosis of S. Typhi from blood cultures taken during the acute phase of the illness, and 50 patients with non-enteric fever (urinary tract infection, malaria, respiratory infection) who had received typhoid and paratyphoid vaccines.

Table 3. Results of the Sensitivity and Specificity of the Tubex and Widal Tests in the Three Groups

Assay	Typhoid n= 50	Non Typhoid Fever n=50	Normal healthy individuals n=100	Senstivity (%)	Specificity (%)
Significant Tubex (>4)	38(76%)	2(4%)	1(1%)	76	96-99
Significant IgG/IgM	36(72%)	5(10%)	6(6%)	72	90-94
Significant Widal Test	34(68%)	2(4%)	1 (1%)	68	96-99

Among the three tests, the Widal test had the lowest sensitivity at 68%, while the Tubex test had the highest sensitivity at 76%. The Tubex test had greater specificity than Typhidot when compared in non-typhoid groups and normal healthy individuals. The advantages of the Tubex TF test over blood cultures are that it requires less time and does not require establishing local cutoff titers as in the Widal test. In countries that can afford the relatively high cost of the Tubex TF test and require a rapid diagnostic kit to support the clinical diagnosis of typhoid fever, the Tubex TF can be recommended. For screening and surveillance purposes and in low-cost settings, the Widal test may be preferred.

CONCLUSION

The Widal, Typhidot, and Tubex-TF serological tests each present distinct advantages and limitations in diagnosing typhoid fever. The Widal test, widely used in developing countries, is prone to cross-reactivity and requires region-specific cut-off titters, which may affect accuracy. Typhidot provides rapid, qualitative results with good sensitivity and specificity and a strong negative predictive value, though it cannot quantify antibody levels and still risks cross-reactivity. Tubex-TF offers semi-quantitative results with good diagnostic performance but challenges arise from subjective interpretation of color-based scoring. Optimal use of these tests depends on clinical presentation, laboratory resources, personnel expertise, turnaround time, and cost. Future research should focus on developing standardized,

objective interpretation criteria and evaluating the performance of combined testing approaches in diverse endemic settings to enhance diagnostic accuracy and clinical utility.

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