

The role of ^{99m}Tc -MIBI scintigraphy in the management of patients with pulmonary tuberculosis

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Abstract. – Background: This study aimed to determine whether ^{99m}Tc -methoxyisobutylisonitrile (MIBI) scanning could improve diagnostic accuracy of pulmonary tuberculosis (PTB) and help clinical decision making for an accurate management.

Material and Methods: ^{99m}Tc -MIBI scintigraphy was performed in 62 cases of PTB 34 cases had active pulmonary tuberculosis (APTB) and were at the beginning of antituberculosis medication (group 1) as well as 28 cases had inactive pulmonary tuberculosis (IPTB) and were post antituberculosis medication (group 2). The qualitative and semiquantitative findings of both scanning methods were assessed. For semiquantitative evaluation, regions of interest (ROIs) were drawn over the lesion (L), non-lesion (NL) and neck soft tissue (NST). The mean count values of ROIs were obtained and L/NL and L/NST were calculated.

Results: Thirty-four patients with APTB (15 males and 19 females; mean age of 47.85 ± 1.91 yrs) and 28 cases with IPTB (9 male and 19 females; mean age of 53.96 ± 2.33 yrs) were included in this study. The sensitivity, specificity, accuracy, positive and negative predictive (PPV and NPV) values of ^{99m}Tc -MIBI were 88.2%, 75%, 82.2%, 81.1% and 84% respectively. The mean value of L/NL in the APTB for ^{99m}Tc -MIBI was 1.45 ± 0.18 and L/NST was 1.57 ± 0.26 which was significant statistically ($p < 0.00$).

Conclusions: The study demonstrated that ^{99m}Tc -MIBI scanning can be complementary to other diagnostic techniques especially in patients with indeterminate APTB and those in whom recurrent disease is suspected. In addition, because of its availability, rather low costs, easy performance, and objective semiquantitative informa-

tion supplied, ^{99m}Tc -MIBI scanning might be establish in routine imaging center to assess the pulmonary tuberculosis. However, further exploration is needed to validate its clinical role.

Key Words:

Pulmonary tuberculosis, ^{99m}Tc -MIBI, Chest x ray, Multidrug-resistant (MDR), Semiquantitative analysis.

Abbreviations

^{99m}Tc -MIBI = technetium-99m-methoxyisobutylisonitrile
PTB = pulmonary tuberculosis
APTB = active pulmonary tuberculosis
IPTB = inactive pulmonary tuberculosis
ROI = regions of interest
L/NL = lesion to non-lesion
L/NST = lesion to neck soft tissue
MDR = multidrug-resistant
FDG PET = fluoro deoxy glucose positron emission tomography
ATC = antitubercular chemotherapy
LEAP = low-energy all purpose
LDH = lactate dehydrogenase
BALF = bronchoalveolar lavage fluid
CXR = chest x ray
EMB = Ethambutol;
SUV = standardized uptake value
BALF = bronchoalveolar lavage fluid

Introduction

Tuberculosis (TB) is dreaded infectious affecting almost every organ of the body¹. The incidence of tuberculosis has ceased to decline in the developing world and in some parts of the developed world mainly resulting from the increased prevalence of human immunodeficiency virus infection and the development of multidrug-resistant (MDR) strains of mycobacterium tuberculosis even after the development of sophisticated researches, high tech drug design and various diagnostic modalities²⁻⁴. Rapid and accurate diagnosis of infected patients is a cornerstone of the global tuberculosis control strategies.

A definite diagnosis of pulmonary tuberculosis can be made with the presence of acid fast bacilli on sputum smear examination which sometimes its result is repeatedly negative for acid fast bacilli. In addition, culture for tubercle bacilli is a sophisticated and time consuming process. Furthermore, problems also faced by clinicians treating tuberculosis are difficulty in distinguishing between active and healed lesions in suspected cases of recurrence and assessment of response to therapy in cases of MDR.

To overcome this difficulty, various workers have tried different biochemical tests and also radiopharmaceuticals such as ^{67}Ga citrate⁵⁻⁸, ^{201}Tl ^{8,9}, radiolabeled monoclonal antibodies⁹, ^{99m}Tc -glucoheptonate^{10,11}, ^{111}In -octreotide^{12,13}, ^{99m}Tc (V)-dimercaptosuccinic acid, ^{99m}Tc -citrate¹⁴, ^{99m}Tc -Ciprofloxacin (Infecton)¹⁵ and ^{99m}Tc -Tetrafosmine¹⁶⁻¹⁸ have been used in the evaluation of tuberculosis, but they all have limitations in clinical settings. The role of fluoro-2deoxy-D-glucose positron emission tomography (FDG PET) and PET/computed tomography (PET/CT) in TB and other inflammatory diseases is evolving and is not as yet clearly defined^{19,20}.

In several *in vitro* and *in vivo* studies, ^{99m}Tc -metoxyisobutylisonitrile (^{99m}Tc -MIBI) scanning²¹⁻²⁶, which is a widely used as a myocardial perfusion agent, has been shown to provide promising results in this connection.

This article as the largest clinical study in nuclear medicine field in this query was conducted to use of ^{99m}Tc -MIBI scanning as compared with clinical, laboratorial-radiological findings in patients with pulmonary tuberculosis (PTB). Moreover, tried to evaluate the feasibility of this radiotracer in routine practice.

Materials and Methods

Participants and Study Design

Sixty two subjects were enrolled in this study and divided in 2 groups. The patients were recruited from the main Tuberculosis Hospital at our country from May 2004 to September 2006. Group 1 including 34 cases with active pulmonary TB (APT_B) and had a previously established diagnosis of pulmonary tuberculosis, according to the clinic, radiography and also sputum smear and culture. The pulmonary tuberculosis was diagnosed before imaging. No patient had taken medication before ^{99m}Tc -MIBI imaging. Group two consist of 28 inactive pulmonary tuberculosis (IPT_B) cases which was considered when sputum culture and smear were both negative after 9 months of antitubercular chemotherapy (ATC).

This study was approved by the institutional Ethics Committee of Shaheed Beheshti University of Medical Science and all patients gave written informed consent.

Imaging

Anterior and posterior planar images of the chest were obtained 20 and 60 min following intravenous injection of 370 MBq (10 mCi) ^{99m}Tc -MIBI for 6 minutes in each set. Images were obtained using a single detector system (ADAC Genesys, Malpitas, CA, USA) with low-energy, all purpose (LEAP) collimator and were recorded in a 256 • 256 • 16 word matrix. To diminish the superimposed scapular and pectoral muscular activities from the field of the lungs, acquisition was carried out in the hands-over head position. Technetium-99m-MIBI scintigraphy assessment of MIBI uptake was done qualitatively (subjectively) and semi-quantitatively and correlated with the radiographs.

Image Analysis

Qualitative and semi-quantitative images were assessed by two nuclear medicine physicians, who were blinded to all other clinical and imaging informations. The interobserver variability was resolved by consensus. Patients showing increased uptake in early or delayed or both early and delayed images were regarded as positive. The ^{99m}Tc -MIBI scan data were compared to the corresponding chest roentgenograms and divided to upper zone, middle zone, lower zone in the patients.

For qualitative grading, the lesion was compared with neck soft tissue (NST) as follows: (mild) abnormal uptake more than NST and less than myocardium; (moderate) abnormal uptake much more than NST and less than myocardium and (severe) abnormal uptake equal to the myocardium.

For determination of lesion-to-background ratio, the geometric mean of anterior and posterior ROI values was used. The lung fields without any lesion were selected as background regions. In addition, lesion to NST ratio as above was calculated. In all analysis, the mean count per pixel was considered.

Statistical Analysis

A 2-tailed t-test was used to compare the mean values between groups. The continuous variables are expressed as the mean \pm SD, and categorical variables as the absolute values and percentages. Student's *t*-test and ANOVA were used to compare differences between continuous variables, and the chi-square test was used for categorical variables. A *p* value and Fisher exact <0.05 were considered to be statistically significant. The statistical analysis was performed with the using of SPSS version 18 (Chicago, IL, USA).

Results

Thirty-four patients with APTB (15 males and 19 females; mean age of 47.85 ± 1.91 yrs) and

28 cases with IPTB (9 male and 19 females; mean age of 53.96 ± 2.33 yrs) were included in this study and underwent ^{99m}Tc -MIBI scintigraphy. There was no statistically difference between age and gender of two groups ($p > 0.05$).

Totally, 30 out of 34 (88.2%) APTB patients had positive ^{99m}Tc -MIBI and 21 out 28 (75%) IPTB cases had negative ^{99m}Tc -MIBI (Figure 1). The sensitivity, specificity, accuracy, positive and negative predictive values were 88.2%, 75%, 82.2%, 81.1% and 84% respectively.

In semi-quantitative analysis of APTB cases, 4 (11.7%) subjects had normal scan; 14 (41.2%), 14 (41.2%) and 2 (5.9%) cases had mild, moderate and severe degrees of ^{99m}Tc -MIBI activity respectively. In addition, in IPTB group, 22 (78.5%) subjects had normal scan; 5 (17.86%) and 1 (3.5%) cases had mild and moderate degrees of ^{99m}Tc -MIBI activity respectively. None of them had severe activity of ^{99m}Tc -MIBI.

APTB patients had 100 lesions on chest x ray but 72 on scan which mostly located in middle and upper zones. Sixty lesions were congruent in chest x ray and scan that 12 lesion was in RU, 16 lesions in RM, 6 in RL, 14 in LU, 11 in LM and 1 in LL (Table I).

In IPTB cases, there were 86 lesions on chest x ray that 11 lesions were active on scanning. Only 9 active lesions on scan were congruent to the chest x ray lesions (Table II).

The mean value of L/NL in the APTB was 1.45 ± 0.18 and L/NST was 1.57 ± 0.26 which

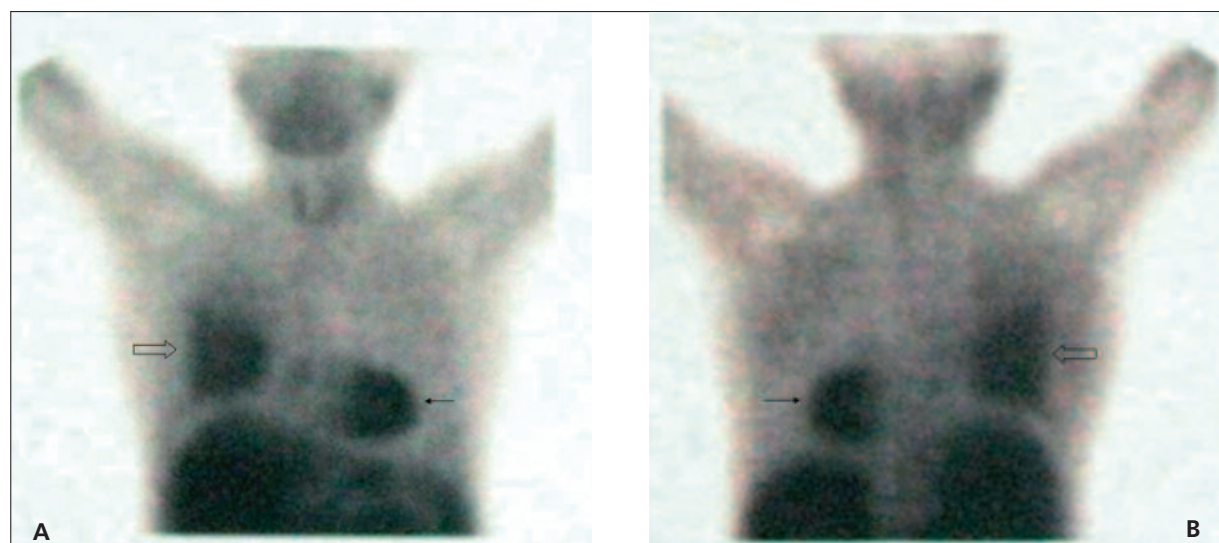


Figure 1. The abnormal activity in the middle lobe of the right lung on the anterior (A) and posterior (B) views of ^{99m}Tc -MIBI scintigraphy of a patient with APTB. The large and small arrows showing pulmonary tuberculosis and heart in the images respectively.

Table I. Distribution of lesions of the APTB patients in the chest x ray and ^{99m}Tc-MIBI scanning.

	Lung lobes	Chest x ray number (%)	Scan number (%)	Common lesion
Right lung	Upper	21 (21%)	14 (19.4%)	12
	Middle	24 (24%)	18 (25%)	16
	Lower	8 (8%)	7 (9.7%)	6
Left lung	Upper	20 (20%)	16 (22.2%)	14
	Middle	22 (22%)	15 (20.8%)	11
	Lower	5 (5%)	2 (2.7%)	1

was significant statistically ($p < 0.00$). The semi-quantitative analysis of two L/NL and L/NST ratios in the APTB patients are described in Table III.

There are no significant differences between the mean value of L/NL ratio and also L/NST ratio in true positive and false positive lesions (1.45 ± 0.18 Vs. 1.39 ± 0.15) and (1.57 ± 0.26 Vs. 1.58 ± 0.24) respectively ($p > 0.05$).

Discussion

There are difficulties in the detection of activation and in the evaluation of treatment response based on the clinical, laboratory and clinical findings in patients with PTB. Early studies showed that ⁶⁷Ga scanning is a sensitive indicator of the presence of active tuberculosis^{27,28}, but the results obtained were controversial.

Siemsen et al²⁸ found that 95% of active or bacteriologically positive patients had abnormal ⁶⁷Ga scans and all of the remaining inactive or bacteriologically negative patients had normal scans. Utsunomiya et al⁷, compared ⁶⁷Ga and ²⁰¹Tl in detection of the activity of PTB and found sensitivity, specificity and accuracy of 83.1%, 60.7% and 74.1%, respectively for ⁶⁷Ga; the same ratios for ²⁰¹Tl were 88%, 82% and 85.6%, respectively.

However, low doses of injected ²⁰¹Tl and ⁶⁷Ga as well as their suboptimal physical characteristics limit their usefulness in this regard.

Experimental scintigraphic studies with radio-labeled polyclonal bacillus Calmette-Guérin (BCG)-specific intact antibody⁹, BCG specific F(ab')₂⁹, In-octreotide¹² and technetium-99m-glucoheptonate^{10,11} appear to be promising for the future for specific localization of PTB.

The favorable imaging characteristics (140 keV peak energy, 6 hr half-life) and shelf availability make ^{99m}Tc-MIBI superior to other radionuclide techniques in investigations of PTB.

In addition, Komori et al²⁹ demonstrated that ^{99m}Tc-MIBI could be distinguish benign lesions from malignant lesions in the pulmonary and mediastinal regions. This study which is largest in sample size in this query, to our knowledge, showed the sensitivity, specificity, NPV and PPV of technetium-99m MIBI scanning in the diagnosis of active PTB were 88.2%, 75%, 84% and 81.1% respectively and the overall accuracy was 82.2% which rather was similar to previous studies (21). On the basis of our results, ^{99m}Tc-MIBI scan also may be of importance in the follow-up of PTB. So, in cured cases of tuberculosis, there was no uptake of ^{99m}Tc-MIBI uptake can also be helpful in patients with recurrent symptoms for whom it is difficult to distinguish between active disease and tubercular sequelae.

Table II. Distribution of lesions of the IPTB patients in the chest x ray and ^{99m}Tc-MIBI scanning.

	Lung lobes	Chest x ray number (%)	Scan number (%)	Common lesion
Right lung	Upper	13 (15.1%)	3 (27.2%)	2
	Middle	23 (26.7%)	2 (18.1%)	2
	Lower	13 (15.1%)	3 (27.2%)	3
Left lung	Upper	9 (10.4%)	1 (9%)	1
	Middle	19 (22%)	2 (18.1%)	1
	Lower	9 (10.4%)		

Table III. The semi-quantitative analysis of two L/NL and L/NST ratios in the APTB patients on ^{99m}Tc -MIBI scanning.

Severity	L/NL	L/NST
Mild	1.36 \pm 0.11	1.47 \pm 0.20
Moderate	1.57 \pm 0.05	1.72 \pm 0.22
Severe	1.93 \pm 0.05	2.14 \pm 0.10

L/NL, the ration of lesion to normal area; L/NST, the ratio of lesion to sternocleidomastoid muscle area.

Onsel and et al²¹ assessed ^{99m}Tc -MIBI scintigraphy in 36 cases which 24 cases had active PTB and 2 had miliary TB and 10 were suspected of having relapsed PTB. In 24 patients with active localized PTB, 22 (92%) showed increased focal uptake of ^{99m}Tc -MIBI, two patients with minimal infiltration on chest radiographs had no accumulation of ^{99m}Tc -MIBI. Both patients with miliary PTB showed diffuse ^{99m}Tc -MIBI uptake in the lungs. Among 10 patients with suspicion of relapse, ^{99m}Tc -MIBI were true-positive in 4 of 5 patients (80%) with culture-proven tuberculosis and false-positive in 2 of 5 (40%) patients with negative sputum cultures.

In a recent study²⁴ in 36 TB cases (24 APTB and 12 IPTB), ^{99m}Tc -MIBI with planar and SPECT mode was performed. They mentioned a sensitivity of 87.5% for planar and 95.8% for SPECT, so they recommended ^{99m}Tc -MIBI SPECT is a useful modality for differentiation of active from inactive pulmonary TB. Furthermore, in a study in 12 cases with APTB and 7 with IPTB, sensitivity was 85.7%³⁰. In another study in 32 cases with APTB, the sensitivity of ^{99m}Tc -MIBI scintigraphy was 87.5% (28/32) and all 14 IPTB had negative scanning²⁶.

The mean value of L/NL ratio was more significantly relative to L/NST ratio by both radiopharmaceuticals in current study indicating the NST region rather than normal lung region as background had a less activity. Therefore, consideration of lesion equal to NST region as a positive scanning may increase the sensitivity which used before¹⁸. In addition, the consideration of normal appearing area in the lung as a background region for analysis may be inappropriate especially in miliary type. We considered a positive finding wherever the intensity was more than NST region activity in both scans.

In Degirmenci et al investigation¹⁸, considerable ^{99m}Tc -tetrofosmin uptake was observed in all 27 patients with APTB, most probably related to

disease activity. Moreover, in 5 of the 6 patients with IPTB (inactive pulmonary tuberculosis), no uptake was detected. Only in 1 of 6 patients with IPTB, there was tetrofosmin uptake.

Kumar et al¹⁶, observed that the tetrofosmin uptake in 12 of 13 (92%) patients with suspected active tuberculosis showed a high degree of correlation with the radiographic findings. In 1 patient (8%), there was bilateral radiotracer uptake (false-positive), whereas the radiograph showed a lesion on 1 side only. Of the 5 treated patients, 4 did not show any radiotracer uptake and 1 had equivocal uptake.

The false negative and positive of our study (15.27%) were also similar to other investigations^{5,31,32}. Lin et al³¹ described two patients with miliary TB which one did not diagnose by chest X ray (CXR) and another did not diagnose by gallium scan. Grief and Lisbona³² described two miliary TB cases with normal CXR and abnormal gallium scan and also Kao et al⁵ reported numbers of extra pulmonary TB during miliary type with normal CXR

The two false negative cases of our caseload had a minimal infiltration on CXR with low lactate dehydrogenase (LDH) of bronchoalveolar lavage fluid (BALF) representing mild inflammation. Onsel et al²¹, observed that ^{99m}Tc -MIBI scans also did not reveal active granulomas in two patients with minimal infiltration on chest roentgenograms and in one patient with recrudescence disease probably due to poor spatial resolution. Moreover, ^{99m}Tc -MIBI scans were false-positive in two of five patients with inactive disease who were suffering from a different pulmonary pathology such as atypical pneumonia and lung cancer. The one false positive case of our study, had infiltration in the CXR at early treatment as well as collapse in the same region in the CXR at end treatment. Out of ten patients with abnormal uptake on the initial scans in Onsel study²¹, just three patients showed no significant scintigraphic changes within 2-3 months, despite clinical and partial radiological regression, indicating the delayed normal scan relative to the clinical and radiographic findings. This aspect may also explain the false positive of other our cases. Sarikaya et al³³ described a case with central brochogenic carcinoma accompanied with atelectasia, that ^{99m}Tc -MIBI scanning uptake was shown either in tumoral and atelectatic regions.

Our work also showed the positive correlation between the extent of ^{99m}Tc -MIBI scanning and CXR abnormalities in PTB and also the number

of lesions in IPTB patients on ^{99m}Tc-MIBI scanning were less than the lesions as detected with CXR which could be related to the CXR demonstration of all sequela and old lesion such as fibrosis. Therefore, in cases with completed antituberculosis chemotherapy (ATC) with had favorable clinical and bacteriological situation without CXR improvement and in cases who suspicious to continue medication or repeated diet, ^{99m}Tc-MIBI scanning may be useful.

In our patients which had miliary and diffuse TB in CXR, depicted false negative on its ^{99m}Tc-MIBI scanning. It suggested that the minimal roles of ^{99m}Tc-MIBI scanning were in patients who had minimal infiltration and also miliary type in CXR. The maximum power of the ^{99m}Tc-MIBI scanning was in the localized PTB. Therefore, it seemed both CXR and ^{99m}Tc-MIBI scanning are necessary in miliary PTB and also ^{99m}Tc-MIBI scanning interpreted carefully in cases with minimal infiltration in CXR.

The semiquantitative indices in our report fail to differentiate true positive from false positive lesions which may be limitation of ^{99m}Tc-MIBI in this issue.

The mechanism of ^{99m}Tc-MIBI uptake can be due to high mitochondrial content of the epithelioid cells in the granulomatous lesions^{21,22}. In a recent *in-vitro* researches^{23,34}, *Mycobacterium tuberculosis* cultures had significantly higher ^{99m}Tc-MIBI uptake compared with fibroblasts and myocytes cultures, which suggests contribution of the bacilli themselves in ^{99m}Tc-MIBI uptake.

In a more specific nuclear medicine modalities efforts for tuberculosis imaging, a suitable ligand i.e. specific first line antitubercular drug ethambutol (EMB)³⁵ was chosen for detection as well as localization of the lesion using nuclear medicine modality which was radiolabeled with ^{99m}Tc. High labeling efficiency (>85%), *in vitro* and *in vivo* stability, biodistribution and pharmacokinetic parameters were consistent with the original drug suggesting that ^{99m}Tc-MIBI was safe for diagnostic use.

In a phase I clinical trial of the ^{99m}Tc-MIBI in 14 patients of pulmonary tuberculosis, ^{99m}Tc-EMB was a specific radiopharmaceutical for imaging tubercular lesions, and relatively safe for human use. It suggested that ^{99m}Tc-EMB detects and locates active sensitive as well as resistant lesions by accumulating in the lesion in rising pattern over time³⁶.

In molecular imaging with FDG-PET, it is currently not possible to differentiate malignant lesions from active tuberculosis consistently. Intense FDG uptake is usually noted in active tuberculous lesions involving the lung parenchyma³⁷⁻⁴⁴ and the high values of standardized uptake value (SUV), up to 21.0 (range 2.2-21.0), in tuberculous lesions were also obtained¹⁹, which is attributed to the presence of a large number of activated macrophages with high glycolytic rate. In addition, to improve its specificity despite high sensitivity, the combined use of F-18 FDG and C-11 acetate, as the latter accumulates in tumors but not in inflammatory lesions has been conducted. However, is needed further clarification⁴⁵. Another study⁴⁶ focused on differentiation of pyogenic from tuberculous infection by F-18 FDG PET. However, combination of PET with CT technique may facilitate differentiation of tuberculosis from malignant lesions.

In future, new and more specific radiotracers, like positron-emitter labeled antituberculous drug molecules may help to differentiate TB from cancer and nontuberculous inflammatory processes.

^{99m}Tc-MIBI scanning has some advantages such as the least invasive, performable even in ill patients and also not affected by the functional state of the lung parenchyma. In addition, it is useful in guiding lung biopsy and in choosing pulmonary segments for BAL as well as use to assess the accuracy of disease in the entire lung as well as in extrapulmonary sites. Furthermore, ^{99m}Tc-MIBI as a most common myocardial perfusion scan agent in all nuclear medicine centers and available more than aforementioned radiotracers and also its use in each working day of a nuclear medicine center, may be preferable approach to pulmonary tuberculosis evaluation⁴⁷. There have been, however, few reports on the evaluation of ^{99m}Tc-MIBI scanning in PTB. Thus, further exploration is needed to validate its clinical role.

In conclusion, this study demonstrated that ^{99m}Tc-MIBI scanning can be complementary to other diagnostic techniques especially in patients with indeterminate APTB and those in whom recurrent disease is suspected. In addition, because of its availability, rather low costs, easy performance, and objective semiquantitative information supplied, ^{99m}Tc-MIBI scanning might be establish in routine imaging center to assess the pulmonary tuberculosis. However, further exploration is needed to validate its clinical role.

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