

Exercise Tolerance Test using Duke Treadmill: An Observational Study in a Private Tertiary Care Hospital

Muhammad Maaz Arif, MBBS; Muhammad Zarrar Arif Butt¹, MBBS, FCPS (Cardiology);
Muhammad Affan Arif Butt², MBBS, FCPS (Pediatrics)

Department of Community Health Sciences, FMH College of Medicine and Dentistry, ¹Department of Cardiology, Fatima Memorial Hospital, ²Department of Pediatrics, Gulab Devi Hospital, Lahore, Pakistan

Received: 14-07-2020
Revised: 02-02-2021
Accepted: 13-03-2021
Published: 22-06-2021

INTRODUCTION

Exercise tolerance test (ETT) also called “exercise stress test” or “exercise treadmill test” is a validated noninvasive test for diagnosing coronary heart diseases in symptomatic patients and also in assessing cardiopulmonary reserves; it is not generally applicable on asymptomatic patients. This test is used to ascertain a safe limit for exercise in patients with stable angina. It is a commonly used test involving a treadmill, blood pressure (BP), and electrocardiogram (ECG) monitoring.^[1,2]

Advantages of ETT include assessing prognostic markers, safety, availability, ease of use, and economic. The test is also useful for identifying whether a patient is at high risk for future adverse events [Table 1]. Disadvantages of ETT include low sensitivity and specificity. Sensitivity ranges from 48% to 94% (mean: 65%), whereas specificity ranges from 58% to 98% (mean: 70%).^[3] Sensitivity and specificity increase after correlating with history, symptoms, BP response, exercise

ABSTRACT

Background: Ischemic heart diseases (IHDs) are one of the most prevalent diseases worldwide. Several tests are undertaken for diagnosing IHDs including electrocardiography (ECG), echocardiography, troponin test, and angiography. Exercise tolerance test (ETT) is an ideal noninvasive test for diagnosing IHDs. ETT is quite useful for risk estimation in patients diagnosed with coronary artery diseases or undergoing vascular surgery. The Duke treadmill score has a great prognostic value for ETT. **Aims:** The study aimed to compare the data between positive, negative, and inconclusive cases undergoing ETT with several variables that are related to cardiac scores, pathologies, and risk factors. **Materials and Methods:** It was a cross-sectional study that included 61 patients undergoing the test. The study was conducted at the cardiology ward, Fatima Memorial Hospital, Lahore, Pakistan. **Results:** The demographic characteristics showed majority of the patients to be male with 44 (72.13%) as opposed to female with 17 (27.87%) cases. The average age of all the cases was 43.48 ± 8.65 . Most of the patients undergoing the test had atypical angina with 55 (88.71%), followed by typical angina with 3 (7.14%) and no angina with 3 (7.14%) cases. Cases showed the past history of positive family reports with 20 (32.79%), followed by a history of smoking with 11 (18.03%), diabetes with 9 (14.75%), catheterization with 7 (11.48%), coronary artery bypass grafting with 5 (8.2%), and myocardial infarction with 5 (8.2%) cases. **Conclusion:** Duke treadmill scores of the three groups revealed that most of the cases (81.97%) fall in the intermediate-risk group (between 4 and - 10 scores) and the standard Bruce protocol showed that majority of the cases only passed Stage II (37.7%) and Stage III (37.7%) of the treadmill. Few studies have been conducted on ETT that shows a detailed analysis of this test with different associated factors. Studies like these will help in conducting greater work of this nature, analyzing important content.

KEYWORDS: Bruce protocol, Duke treadmill, exercise tolerance test, ischemic heart diseases

capacity, and use of other investigations such as ECG, echocardiography, and nuclear myocardial perfusion imaging. ETT is quite useful for risk estimation in patients diagnosed with coronary artery diseases (CADs) or undergoing vascular surgery. The Duke treadmill score has excellent prognostic value for exercise stress testing.^[4]

This study aimed to analyze and determine the demographic characteristics, past history, and treadmill test details and to compare ETT test results among positive, negative, and inconclusive cases. The present study will help in the analysis of demographic variables, angina types, past history, ECG

Address for correspondence: Dr. Muhammad Maaz Arif, Department of Community Health Sciences, FMH College of Medicine and Dentistry, Lahore, Pakistan.
E-mail: maazarifbutt@gmail.com

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Arif MM, Arif Butt MZ, Arif Butt MA. Exercise tolerance test using duke treadmill: An observational study in a private tertiary care hospital. *J Clin Prev Cardiol* 2021;10:68-73.

Access this article online

Quick Response Code:



Website: www.jcpconline.org

DOI: 10.4103/JCPC.JCPC_48_20

Table 1: High risk predicted with exercise tolerance test

Incapability to complete 6 min of Bruce protocol
Early positive test (≤ 3 min)
Strong positive test (ST depressions ≥ 2 mm)
Prolonged ST depression ≥ 3 min after stopping exercise
Downsloping ST depression
Ischemia at low heart rate (≤ 120 beats/min)
Low blood pressure response
Serious ventricular arrhythmia at heart rate ≤ 120 beats/min

Table 2: Indications for exercise tolerance test

Diagnosing CAD
Risk assessment and prognosis in suspected CAD
Evaluating vasospastic and unstable angina
Prognostic assessment after myocardial infarction
Detecting myocardial ischemia
Assessing clinically chronic artery stenosis
Cardiac rehabilitation program
CAD=Coronary artery disease

abnormalities, and treadmill test details among different cases with a detailed examination of the ETT details between positive, negative, and inconclusive cases. The study will also help in encouraging greater research on ETT and other noninvasive cardiac tests.

Review of literature

ETT is a relatively safe test. According to a national survey of exercise stress testing facilities, myocardial infarction or mortality can be expected in 1 per 2500 tests. All persons conducting exercise stress tests should be trained on how to diagnose and manage complications if they arise. Emergency resuscitation equipment and drugs should also be readily available.^[5]

Before carrying out an ETT, it is important to have awareness about the ETT protocol. The initial evaluation of all patients advised to perform ETT is to be done by a doctor on duty to determine the physical capability and condition of the patient. Resting 12-lead ECG, vitals, and blood sugar levels are mandatory to be done by the staff for all patients. The patient should be accompanied by at least one attendant and he should be properly instructed. Emergency medication and DC cardioverter in a functional position should be available before starting the test. Physical aspects of patient preparation such as the shaving of chest hair and electrode attachment are to be done by technicians and ward boys.^[6,7]

The indications for ETT include diagnosing CAD, risk stratification, functional class assessment, and prognosis in patients with suspected CAD. To evaluate patients with vasospastic angina and unstable angina after they have been stabilized. In patients with history of myocardial infarction, it is used for prognosis assessment, physical activity prescription, or evaluation of current medical treatment. ETT is used for detecting myocardial ischemia in patients considered for revascularization. It is also used for detecting patients with chronic aortic stenosis, to assess functional capacity and

symptomatic responses and as part of cardiac rehabilitation programs [Table 2].^[8] The contraindications of ETT are classified as absolute and relative contraindications. The absolute indications include the inability to exercise and major heart pathologies such as myocardial infarction, unstable angina, endocarditis, myocarditis, pericarditis, aortic dissection, and decompensated heart failure. Relative contraindications incorporate complete heart block, hypertrophic obstructive cardiomyopathy, main CAD, recent stroke, and resting systolic BP >200 mmHg or diastolic blood pressure >110 mmHg.^[2,9] The indications for stopping ETT can also be divided into absolute and relative indications. The absolute indications include suspicion of myocardial infarction, the onset of angina, drop in systolic BP with increasing workload, signs of poor perfusion, severe shortness of breath, central nervous system symptoms, and serious arrhythmias. The relative indications involve any chest pain, physical or verbal manifestations of short of breath, wheezing, severe fatigue, pronounced ECG changes, and intermittent claudication [Table 3].^[10,11]

It is important to know about the operations and scores of ETT. Duke treadmill score is a very efficient scoring system and a good prognostic test for ETT.

Duke treadmill score = (Exercise duration [minutes]) – (5 × ST deviation [mm]) – (4 × angina index)

Angina index: 0 = no angina, 1 = nonlimiting angina, and 2 = exercise limiting angina.

Duke treadmill score: ≥ 5 indicates low risk for cardiovascular events, ≤ -11 indicates high risk for cardiovascular events, and between 4 and -10 indicates intermediate risk.^[12,13]

The standard Bruce protocol is used for ETTs.^[14] Its outcomes are well validated, and exercise capacity measured in metabolic equivalents (METs) has a good prognostic value [Table 4].^[15,16] One MET is defined as the amount of oxygen consumed while sitting at rest and is equal to 3.5 ml O₂ per kg body weight × min. The MET concept represents a simple, practical, and easily understood procedure for expressing the energy cost of physical activities as a multiple of the resting metabolic rate.^[17] ETT also incorporates data from heart rate, systolic and diastolic pressure, ST elevation, ST depression, ST/HR index, premature ventricular contractions (PVCs), and functional aerobic impairment (FAI) %.^[18,19]

For distinguishing positive and negative cases of ETT, it is important to know the criteria of positive tests. The criteria of positive ETT test include downsloping ST depression of at least 1 mm, ST elevation, increase in QRS voltage, failure of BP to rise during exercise, ventricular arrhythmias, and inability to increase heart rate.^[20]

MATERIALS AND METHODS

Study area, population and design

The cross-sectional study was conducted in the Department of Cardiology, Fatima Memorial Hospital, Lahore, Pakistan. The study included 61 patients undergoing ETT for 6 months from January 2018 to June 2018.

Table 3: Contraindications and indications for stopping exercise tolerance test

Absolute contraindications	Relative contraindications	Absolute indications for stopping ETT	Relative indications for stopping ETT
Myocardial infarction	Complete heart block	Suspicion of myocardial infarction	Any chest pain that is increasing
Unstable angina	Hypertrophic obstructive cardiomyopathy	Onset of moderate-to-severe angina	Physical or verbal manifestations of short of breath
Endocarditis	Main coronary artery disease	Drop-in systolic blood pressure with increasing workload	Wheezing
Myocarditis	Recent stroke	Signs of poor perfusion (pallor, cyanosis, cold-clammy skin)	Severe fatigue
Pericarditis	Resting systolic blood pressure >200 mmHg	Severe shortness of breath	Pronounced ECG changes
Aortic dissection	Resting diastolic pressure >110 mmHg	CNS symptoms (ataxia, vertigo, confusion, visual or gait problems)	Intermittent claudication
Decompensated heart failure		Serious arrhythmias (second- or third-degree atrioventricular block, atrial fibrillation, or sustained ventricular tachycardia)	Exercise-induced bundle branch block
Inability to exercise		Technical inability to monitor ECG Patient's request to stop	Less serious arrhythmias such as supraventricular tachycardia

ETT=Exercise tolerance test, ECG=Electrocardiography, CNS=Central nervous system

Table 4: Standard Bruce protocol

Protocol	Miles per hour	Grade (%)	METs
Stage I	1.7	10	4
Stage II	2.5	12	7
Stage III	3.4	14	10
Stage IV	4.2	16	13
Stage V	5.0	18	15
Stage VI	5.5	20	17
Stage VII	6.0	22	>17

METs=Metabolic equivalents

Sampling technique

A systematic random sampling technique was used and data were analyzed using SPSS software (IBM SPSS Statistics 23).

Data collection

Secondary data were collected via hospital records. All cardiac patients advised by consultants to undergo the treadmill test were included in the research. For qualitative variables, frequencies and percentages were used, whereas for quantitative variables, averages and mean deviations were calculated. Chi-square and ANOVA tests were used for checking significance for variables with P value significant at <0.05 . Ethical review committee permission was undertaken with final approval from the head of department.

RESULTS

For better comparison among the study cases, the groups were divided into positive, negative, and inconclusive cases. The present study showed that there were a total of 61 cases undergoing ETTs with positive cases diagnosed at 12 (19.67%), negative cases at 42 (68.85%), and inconclusive cases at 7 (11.48%).

The demographic characteristics of the present study showed that the majority of the patients were male with 42 (72.13%) as opposed to female with 17 (27.87%)

cases. The gender comparison among the cases showed no significance ($P = 0.25$) [Table 5]. The age distribution of all the cases showed an average age of 43.48 ± 8.65 years. Most of the patients belonged to the age group of 45–59 years with 25 (40.98%) cases, followed by 30–44 years with 23 (37.7%), <30 years with 9 (14.75%), and ≥ 60 years with 4 (6.56%) cases. The age comparison among the cases showed no significance ($P > 0.05$) [Table 6].

As far as types of angina are concerned, the majority of the cases had features of atypical angina with 55 (88.71%), followed by typical angina with 3 (7.14%) and unknown/none with 3 (7.14%) cases. For types of angina, in comparing all the cases, the results showed no significance ($P > 0.05$) [Table 7].

On abnormal findings among the cases, abnormal ECGs recorded were 9 (14.75%) whereas hypertensive cases were 10 (16.39%). No significance ($P > 0.05$) was appreciable for the three groups with respect to abnormal ECG or hypertension [Table 8].

Past history displayed that many cases showed positive family reports with 20 (32.79%) cases, followed by a history of smoking with 11 (18.03%), diabetes with 9 (14.75%), catheterization with 7 (11.48%), coronary artery bypass grafting with 5 (8.2%), and myocardial infarction with 5 (8.2%) cases. On the comparison between the three groups, results showed no significance ($P > 0.05$) for all past history variables [Table 9].

Duke treadmill scores of the three groups revealed that most of the cases with 50 (81.97%) cases were in the intermediate-risk group (between 4 and – 10 scores), 11 (18.03%) cases were in the high-risk group, whereas no cases were in the low-risk group. Standard Bruce protocol revealed that most of the cases were in Stage II and Stage III with 23 (37.7%) and 23 (37.7%) cases each, followed by Stage IV with 10 (16.4%), Stage I with 4 (6.5%), and Stage V with 1 (1.6%) and no cases in Stage VI or Stage VII [Table 10].

Table 5: Demographic characteristics I: Displaying gender distribution and gender ratio

Cases	Number of cases (n)	Males (n)	Females (n)	Male-to-female ratio	Significance (P)
Positive cases	12	7	5	1.40	0.25
Negative cases	42	33	9	3.67	
Inconclusive cases	7	4	3	1.33	
Total, n (%)	61	44 (72.13)	17 (27.87)	2.59	

Table 6: Demographic characteristics II: Displaying age distribution and average age

Cases	Age <30	Age 30-44	Age 45-59	Age ≥60	Average age±mean deviation	Significance (P)
Positive cases (n=12)	2	4	6	0	42.33±8.33	P=0.07
Negative cases (n=42)	7	18	14	3	42.83±8.9	
Inconclusive cases (n=7)	0	1	5	1	47.17±5.76	
Total (n=61), n (%)	9 (14.75)	23 (37.7)	25 (40.98)	4 (6.56)	43.48±8.65	

Table 7: Angina index

Cases	Typical angina	Atypical angina	None/unknown	Significance (P)
Positive cases (n=12)	1	11	0	0.72
Negative cases (n=42)	2	37	3	
Inconclusive cases (n=7)	0	7	0	
Total (n=61), n (%)	3 (7.14)	55 (88.71)	3 (7.14)	

Table 8: Comparison with abnormal findings

Cases	Abnormal ECG	Hypertensive
Positive cases (n=12)	3	4
Negative cases (n=42)	4	5
Inconclusive cases (n=7)	2	1
Total (n=61), n (%)	9 (14.75)	10 (16.39)
Significance (P)	0.23	0.21

ECG=Electrocardiography

Table 9: Past history comparison

Cases	Diabetes	Smokers	Family history	Myocardial infarction	CABG	Catheterization
Positive cases (n=12)	3	2	6	2	1	3
Negative cases (n=42)	5	8	10	2	3	2
Inconclusive cases (n=7)	1	1	4	1	1	2
Total (n=61), n (%)	9 (14.75)	11 (18.03)	20 (32.79)	5 (8.20)	5 (8.20)	7 (11.48)
Significance (P)	0.72	0.80	0.24	0.57	0.86	0.15

CABG=Coronary artery bypass grafting

The treadmill test details I compared the mean of duration, maximum speed, grade, Duke treadmill score, and METs of the three groups. No significance ($P > 0.05$) was appreciated on comparing Duke treadmill scores between the cases, whereas significance ($P < 0.05$) was seen on comparing results for duration, maximum speed, grade treadmill, and METs. Results showed that positive cases predictably seemed to display the lowest mean duration (5.00), lowest maximum speed (2.67), lowest grade treadmill (12.33), and lowest METs (6.34), whereas the mean Duke treadmill score was reported between 4 and - 10 for all three groups (intermediate risk) [Table 11].

The treadmill test details II showed the relation between the means of target heart rate, systolic pressure, and diastolic pressure of the three categories. No significance ($P > 0.05$) was appreciated on comparing the group cases for target

heart rates, maximum systolic blood pressure, and maximum diastolic pressure, whereas significant test results ($P < 0.05$) were displayed for comparing percentage target heart rates and (maximum heart rate × BP)/100. Inconclusive cases showed the lowest mean percentage heart rate (82.17) and the lowest mean (maximum heart rate × BP)/100 (202.12). This seems like an anomaly as positive cases should have been expected to show the lowest of the two rates. This anomaly may suggest limitation of data or a hidden confounding factor that may not be appreciable in the relation between the rates and the cases [Table 12].

Finally, treadmill test details III showed the findings among cases associated with treadmill test about means of maximum ST elevation, maximum ST depression, ST/HR index, PVCs, and FAI %. Results showed no significant findings ($P > 0.05$) on

comparison among cases for maximum ST depression, PVCs, or FAI %, whereas significance ($P < 0.05$) was seen for maximum ST elevation and ST/HR index. Positive cases, as expected, showed the lowest ST elevation and highest ST/HR index [Table 13].

CONCLUSION

The present study showed the comparison of data for ETTs

among positive, negative, and inconclusive cases. Duke treadmill scores of the three cases revealed that most of the cases (81.97%) were in the intermediate-risk group (between 4 and -10 scores), and the standard Bruce protocol revealed that many cases only passed Stage II (37.7%) and Stage III (37.7%) of the treadmill.

Few studies have been conducted on exercise stress testing that shows a detailed analysis of ETT with different associated

Table 10: Duke treadmill scores and standard Bruce protocol

Duke Treadmill Scores				
Scores	Positive cases (n)	Negative cases (n)	Inconclusive cases (n)	Total, n (%)
≥5 (low risk)	0	0	0	0
Between 4 and -10 (intermediate risk)	10	33	7	50 (81.97)
≤-11 (high risk)	2	9	0	11 (18.03)
Standard Bruce protocol				
Stage	Positive cases (n)	Negative cases (n)	Inconclusive cases (n)	Total, n (%)
Stage I	3	1	0	4 (6.5)
Stage II	5	13	5	23 (37.7)
Stage III	3	18	2	23 (37.7)
Stage IV	1	9	0	10 (16.4)
Stage V	0	1	0	1 (1.6)
Stage VI	0	0	0	0
Stage VII	0	0	0	0

DTS=Duke treadmill score

Table 11: Treadmill test details I: Comparison of groups in relation to Duke treadmill score, grade treadmill, duration, maximum speed, and metabolic equivalents

Cases	DTS	Grade (treadmill)	Duration in minutes	Maximum speed	METs
Positive cases	-4.25	12.33	5.00	2.67	6.34
Negative cases	-5.96	13.81	6.81	3.29	8.02
Inconclusive cases	-1.33	12.67	5.06	2.8	6.41
Average	-5.09	13.39	6.25	3.11	7.50
Significance (P)	0.37	0.01	0.02	0.01	0.02

DTS=Duke treadmill score, METs=Metabolic equivalents

Table 12: Treadmill test details II Comparison of groups in relation to target heart rate, percentage heart rate, maximum systolic pressure, maximum diastolic pressure, and (maximum heart rate × blood pressure)/100

Cases	Target HR	Percentage target HR	Maximum systolic pressure	Maximum diastolic pressure	(Maximum HR × blood pressure)/100
Positive cases	174.33	88.75	162.92	97.92	223.85
Negative cases	175.0	94.07	170.83	97.26	254.99
Inconclusive cases	167.83	82.17	161.67	90.83	202.12
Average	174.05	91.66	168.22	96.65	242.80
Significance (P)	0.13	0.00	0.34	0.53	0.01

HR=Heart rate

Table 13: Treadmill test details III: Comparison of groups in relation to maximum ST elevation, maximum ST depression, ST/heart rate index, premature ventricular contraction, and functional aerobic impairment percent

Cases	Maximum ST elevation (mV)	Maximum ST depression (mV)	ST/HR index	PVCs	FAI %
Positive cases	1.23	1.61	3.55	1.00	81
Negative cases	3.00	1.10	1.57	14.81	73
Inconclusive cases	1.33	1.18	1.69	4.83	81
Average	2.46	1.21	1.97	10.95	75
Significance (P)	0.00	0.89	0.02	0.27	0.39

PVCs=Premature ventricular contractions, FAI=Functional aerobic impairment, HR=Heart rate

factors. Studies like these will help in conducting greater work of this nature, analyzing its information for important content.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Arbab-Zadeh A. Stress testing and non-invasive coronary angiography in patients with suspected coronary artery disease: Time for a new paradigm. *Heart Int* 2012;7:e2.
2. Garner KK, Pomeroy W, Arnold JJ. Exercise stress testing: Indications and common questions. *Am Fam Physician* 2017;96:293-9.
3. Griffin BP, Topol EJ. *Manual of Cardiovascular Medicine*. 2nd Edition. Cleveland, Ohio: Lippincott Williams & Wilkins; 2004.
4. Sharma K, Kohli P, Gulati M. An update on exercise stress testing. *Curr Probl Cardiol* 2012;37:177-202.
5. Stuart RJ Jr., Ellestad MH. National survey of exercise stress testing facilities. *Chest* 1980;77:94-7.
6. Suzuki K, Hirano Y, Yamada H, Murata M, Daimon M, Takeuchi M, *et al.* Practical guidance for the implementation of stress echocardiography. *J Echocardiogr* 2018;16:105-29.
7. Davis G, Ortloff S, Reed A, Worthington G, Roberts D. Evaluation of technician supervised treadmill exercise testing in a cardiac chest pain clinic. *Heart* 1998;79:613-5.
8. Levine GN. *Cardiology Secrets*. 3rd Edition. Houston, TX: Mosby; 2010.
9. Vilcant V, Zeltser R. *Treadmill Stress Testing*. Treasure Island (FL): StatPearls Publishing; 2019.
10. Kharabsheh SM, Al-Sugair A, Al-Buraiki J, Al-Farhan J. Overview of exercise stress testing. *Ann Saudi Med* 2006;26:1-6.
11. Hill J, Timmis A. Exercise tolerance testing. *BMJ* 2002;324:1084-7.
12. Lairikyengbam SK, Davies AG. Interpreting exercise treadmill tests needs scoring system. *BMJ* 2002;325:443.
13. Bourque JM, Beller GA. Value of exercise ECG for risk stratification in suspected or known CAD in the era of advanced imaging technologies. *JACC Cardiovasc Imaging* 2015;8:1309-21.
14. Cilli A, Batmaz F, Demir I, Boz A, Toprak E, Ozdemir T, *et al.* The diagnostic yield of exercise stress testing as a screening tool for subclinical coronary artery disease in patients with moderate to severe obstructive sleep apnea. *J Clin Sleep Med* 2011;7:25-9.
15. Gheydari ME, Jamali M, Hajsheikholeslami F, Yazdani S, Jamali M. Value of exercise tolerance testing in evaluation of diabetic patients presented with atypical chest discomfort. *Int J Endocrinol Metab* 2013;11:11-5.
16. Kokkinos P, Kaminsky LA, Arena R, Zhang J, Myers J. New generalized equation for predicting maximal oxygen uptake (from the fitness registry and the importance of exercise national database). *Am J Cardiol* 2017;120:688-92.
17. Jetté M, Sidney K, Blümchen G. Metabolic equivalents (METs) in exercise testing, exercise prescription, and evaluation of functional capacity. *Clin Cardiol* 1990;13:555-65.
18. Abbott JA, Tedeschi MA, Cheitlin MD. Graded treadmill stress testing. Patterns of physician use and abuse. *West J Med* 1977;126:173-8.
19. Pinkstaff S, Peberdy MA, Kontos MC, Finucane S, Arena R. Quantifying exertion level during exercise stress testing using percentage of age-predicted maximal heart rate, rate pressure product, and perceived exertion. *Mayo Clin Proc* 2010;85:1095-100.
20. Llewelyn H, Ang HA, Lewis K, Al-Abdullah A. *Oxford Handbook of Clinical Diagnosis*. USA: Oxford University Press; 2014.