Research Article

Normal Reference Interval of WBC Count After On - Pump Coronary Artery Bypass Graft; When Values Could Be Misleading

Fardin Yousefshahi,[1,2,] [*] Mohammadali Boroumand,[3] Katayoun Haryalchi,[2,4] Jayran Zebardast,[5] Azin Ghajar,[6] and Ehsan Bastan Hagh[7]

[1]Department of Anesthesiology, Pain and Critical Care, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran
[2]Brain and Spinal Cord Injury Research Center, Neuroscience Institute, Tehran University of Medical Sciences, Tehran, Iran
[3]Department of Pathology and Lab Medicine, Tehran Heart Center, Tehran University of Medical Sciences, Tehran, Iran
[4]Department of Anesthesiology, Reproductive Health Research Center, Guilan University of Medical Sciences, Rasht, Iran
[5]Department of Research, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran
[6]Faculty of Medicine, Tehran University of Medical Sciences, Tehran, Iran
[7]Department of Anesthesiology, Pain and Critical Care, Yas Hospital, Tehran University of Medical Sciences, Tehran, Iran

[*] Corresponding author: Fardin Yousefshahi, MD, Brain and Spinal Cord Injury Research Center, Neuroscience Institute, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran. Postal Code: 6114185, Tel: +98-2166591321, Fax: +98-2166591318, E-mail: yousefshahi@tums.ac.ir

Abstract

Background: Applying the cardiopulmonary pump produces inflammatory responses and induces leukocytosis. White Blood Cell (WBC) count has a diagnostic value for detecting different infections. In this study, we want to redefine the normal value reference intervals of WBC count in Coronary Artery Bypass Graft (CABG) patients, to prevent misdiagnose leukocytosis as a sign of infection.
Methods: In an observational study, 140 patients who underwent on - pump CABG were enrolled to find out normal values of the reference interval. WBC counts were evaluated for all of them one day before the operation, first 30 minutes of ICU entrance, after 24 hours, and 48 hours after operation. Normal values of reference intervals were calculated for each measurement by two different statistical methods.
Results: There were 102 men and 38 women with age average of 61 years. There was no significant difference between genders' WBC counts before operation (P = 0.151), ICU entrance (P = 0.391), 24 hours after surgery (P = 0.698), and 48 hours after surgery (P = 0.523). The mean values of WBC after surgery were higher than the normal range of reference interval and had an increasing trend in the first 48 hours after surgery. The WBC values were significantly different between pre and post operation (before operation and ICU admission (P = 0.001), ICU admission and 24 hours later (P = 0.001), 24 hours after surgery, and 48 hours after surgery (P = 0.001)). All post - operative reference values were significantly higher than the range for the general population.
Conclusions: There is a significant increase in WBC count after on - pump CABG. The normal range of WBC should be revised and adjusted to prevent misinterpretation as a sign of infection.

Keywords: White Blood Cell (WBC), Coronary Artery Bypass Graft (CABG), Reference Value

1. Background

Despite advances in perfusion, anesthetic, and surgical techniques, cardiopulmonary bypass (CPB) is still reported to evoke inflammatory reactions (1, 2). The inflammatory response produced by cardiothoracic surgery has been well known for many years; it is due to exposure of blood to non - physiologic surfaces and it occurs in cases in which CPB is applied (1, 3, 4). White blood cell (WBC) count increases as a part of inflammatory response cascade (1, 5, 6).

In another side, leukocytosis is a well - known para - clinical sign in diagnostic criteria for hospital - acquired infections like pneumonia and catheter - related infections,

by Centers for Diseases Control and Prevention (7, 8). Nosocomial infections still represent a serious problem among surgical patients (9). For example, pneumonia is the second most common nosocomial infection in critically ill patients (10). Hospital - Acquired Pneumonia (HAP) complicates 8% to 28% of patients receiving mechanical ventilation with a mortality rate from 24% to 50% and can reach 76% in some specific settings (11). Although the mortality rate has decreased in recent years, it is a major cause of death, morbidity, and resources utilization (11-13). This type of infection can also appear early in the postoperative period after coronary artery bypass graft (CABG); rarely does it account for a prolonged recovery time, a delayed hospi-

tal discharge, and increased costs (14, 15). In the post - operative phase of CABG, correct diagnosis of such an infection could be critically important. As in the Centers for Disease Control and Prevention (CDC) for pneumonia, one of the signs and symptoms are Leukopenia ($\leq$ 4000 WBC/mm^3) or leukocytosis (> 12000 WBC/mm^3) (16). At the same time, other signs and symptoms applicate in the pneumonia criteria could occur in CABG patients frequently, however, it is not related to infections (17, 18). The same talk could be considered about forms of infection, too. These could be the results of Cardiopulmonary Pump Bypass (CPB) induced Systemic Inflammatory Response Syndrome (SIRS) (2), which could affect functions of other organs, too (18, 19). Finally, an important concern about the post CABG patient is the differentiation between infection - related signs and other noninfectious ones.

Then, it seems that without a correct estimation of normal WBC count in post CABG patients, the application of different diagnostic criteria for hospital - acquired infections is impossible. We suggested that as other organ systems, blood and WBC's are affected by the systemic inflammatory reaction, even in non - complicated CABG case. This could affect our insights about the usefulness of some diagnostic criteria for infectious diseases, seriously.

This study aims to determine the normal values of WBC in non - complicated on - pump post CABG patients in first postoperative days.

2. Methods

The study was a single centre prospective observational study, which has been carried out in the Tehran Heart Centre, Tehran University of Medical Sciences, Tehran, Iran in 2013. A total of 140 patients who underwent on - pump CABG and had been proved to have the study criteria have been chosen, randomly. Sample size had been defined based on the Clinical and Laboratory Standards Institute (CLSI) recommendation; it was appropriate to have a confidence limit equal to 90% (20). The inclusion criteria included on - pump CABG patients who do not receive corticosteroid or cardiac inotropic medications; do not have any other cardiac pathology like severe heart valvular disease or congenital heart diseases; do not have synchronic heart valvular surgeries; do not have intra - aortic balloon pump, central or arterial intravascular line or Foley catheter in preoperative phase; do not have ejection fraction < 30%; do not have, suspected or treated for pre - operation infection, or had a surgery in last 3 months; do not have immune deficiency; hematologic disorders malignancy or pre - operation abnormal blood cell count; and do not have severe renal disorder and autoimmune diseases. Also, the patient did not receive

blood products transfusion before the surgery. The exclusion criteria included proved or probable infection needs treatment within one week after surgery, new cardiac pathology, intra - aortic balloon pump and corticosteroid or inotrope receivers. All study cases would have a smooth non - complicated post - operative phase, to remain in the study. Not only all proved cases of infection and infarction were excluded, but also all probable cases who had a medical condition or even those who had such a problem as a differential diagnosis. To attain this monitoring, daily re - assessment of patients during the admission and performing lab and paraclinical tests were considered as indicated. Those who need extra support or treatment including hemodynamic or antibiotics were considered as the exclusion criteria.

WBC count has been checked for the patient the day before surgery, at the time of intensive care unit (ICU) entrance (first 30 minutes), the day after, at the morning, and daily, after that. WBC counts have been done by Cell Counter, "Sysmex kx 21" in Tehran Heart Centre laboratory.

The sample size was calculated based on CLSI guidelines to provide a 90% confidence interval limit (20). Confounders effects were minimized by application of a restricted inclusion and exclusion criteria and using single race and application of the same medical care during the study. To prove eligibility for the cases to be enrolled in the study and assess the inclusion and exclusion criteria and medical records, the patient's charts and hospital database were used.

In case of unidentified infection, patients were excluded from the study before surgery and replaced with the next patient.

By finalizing patient's lists and records, Medcalc software was used to calculate the reference interval. The reference interval for the WBC was determined in this study and the reference interval indicated represents the spectrum of the WBC that is considered normal for each measurement section.

Then, using the *t* - test, the obtained data were compared and then the results were analyzed using SPSS analysis software.

3. Results

Of all 140 patients, there were 102 male and 38 female. In total, the age average was 61.11 ($\pm$ 8.349) years and 39 and 78 years for the youngest and oldest, respectively.

Table 1 represented that gender do not affect the WBC average.

According to Table 2, the WBC rise is visible on the day before surgery (Mean = 7889), when entering the ICU (Mean = 10029), and also on the first day after surgery (Mean =

Table 1. Comparison of the Mean of WBC between Genders[a]

Measurement Time	Men (N = 102)	Women (N = 38)	Total (N = 140)	P Value
Pre - operation	7751.37 (1883.06)	8260.00 (1768.18)	7889.428 (1860.18)	0.151
ICU entrance	10161.08 (3056.92)	9676.57 (2691.57)	10029.57 (2960.62)	0.391
After 24 hours	12032.55 (3786.82)	11810.52 (2648.25)	11972.28 (3506.62)	0.698
After 48 hours	11343.04 (3732.26)	11001.84 (2365.71)	11250.43 (3410.95)	0.523

Abbreviation: ICU, intensive care unit.

[a] Table represented that gender do not affect the WBC average and values are Mean (Standard Deviation).

11972); however, on the second day after surgery (Mean = 112500), the WBC level is slightly reduced.

Also, in this study, it was proved that by eliminating the gender - related confounding effect, the age had no significant effect on WBC changes (P value = 0.278).

Reference intervals and 90% confidence interval for pre - operative, post - operative ICU entrance, 24 hours after surgery, and after 48 hours are presented in Table 2.

Table 3 reveals the values and comparison of differences between each measurement to assess the statistical significance of differences during the time.

The WBC level has risen from the day before surgery to one day after surgery and then shows a slight but statistically meaningful decrease until the second day.

According correlation analysis between "CPB time" and "WBC increase", with increasing pump time, parallel increase was seen in WBC level during pre - operative WBC (R = 0.435, P ≤ 0.0001), post - operative ICU entrance (R = 0.305, P ≤ 0.0001), 24 hours after surgery (R = 0.390, P ≤ 0.0001), and 48 hours after surgery (R = 0.575, P ≤ 0.0001).

4. Discussion

The WBC count is reported to pass the upper limits of general population reference interval, after on - pump cardiac surgery in several studies (21). However, there is no clear report about the normal interval range of WBC in cardiac surgery patients.

Due to its association with some comorbidities (22), including more that studied the atrial fibrillation (21), leukocytosis, is more important in cardiac patients. However, its misleading diagnostic effects are more prominent, when considering the high prevalence of other clinical or laboratory signs and symptoms of infection and sepsis in cardiac surgery.

The inflammatory response after on - pump CABG can be detected from early ICU entrance, it increases in the first 24 hours and decreases gradually after 48 hours (6). The leukocytosis is a known laboratory marker of an inflammatory response, too (6).

Hypoxemia is also common in the CABG patient and they are regarded as a sign of pneumonia or even sepsis and differentiating from the ARDS (18, 23).

Fever is known as a common infection's sing after any surgical technique and may be seen in up to 50% of surgical patients. This postoperative fever is reported in all types of surgeries including those who were undergoing CABG surgeries (24). In a study by Rostami et al., a fever was reported in 29.9% of CABG patients (25). A fever immediately after cardiopulmonary bypass surgery is associated with cognitive impairment, after CABG (26, 27), which potentially could be considered as a sepsis sign itself.

This fever associated with the rise in WBC count could be regarded as a serious infection, which mandates early management including antibiotic therapy.

Acute exacerbation of inflammatory biomarkers is common in infectious diseases as well as the non - infectious inflammatory response, which always happens in on-pump CABG patients in various level of intensity (28).

Moreover, ICU admission, hospitalization, and mechanical ventilation enhance the risk of hospital - acquired infections like VAP and bacteremia (29). This means CABG patients include high - risk patients for infection and needs more attention in this regard, too.

Considering that the WBC count is a very common test for most of the infections and accounting the occurrence of leukocytosis due to inflammatory processes after on - pump CABG, the higher prevalence and risk of infection in this group of patients, and higher occurrence of other signs and symptoms of infection -due to non - infectious causes-, more caution is needed to differentiate various infections and inflammation responses, including WBC count.

As a conclusion, based on this study, the normal range for WBC after on - pump CABG overlaps the CDC criteria for detecting infections, i.e.; pneumonia and other hospital - acquired infections. While none of the patients in this study previously had or developed an infection in the first postoperative week, it is necessary to revise the normal WBC range in the special group of patients, i.e.; on - pump CABG patients, as shown in this study.

Table 2. Reference Intervals and 90% Confidence Interval for Different WBC Measurements[a]

	Minimum	[90% CI] of Minimum	Maximum	[90% CI] of Maximum
Pre - operative WBC	4812.5	[4543.8 - 5097.1]	12235	[11552.3 - 12959.0]
Post - operative ICU entrance	4226.9	[3512.3 - 4941.5]	15832.3	[15117.7 - 16546.9]
24 hours after surgery	6641.5	[6206.9 - 7106.6]	19935.6	[18631.1 - 21331.6]
After 48 hours	6022.3	[5606.3 - 6469.1]	19257.5	[17927.3 - 20686.3]

Abbreviations: WBC, white blood cell; CI; confidence interval; ICU, intensive care unit.
[a]Table represents the reference intervals and 90% confidence interval for pre - operative, post - operative ICU entrance, 24 hours after surgery and after 48 hours.

Table 3. Mean Differences between WBC Counts at Different Times[a]

	Minimum	Maximum	Differences[b]	P Value[c]
Pre - operation - ICU entrance	-1684.69	2595.59	-2140.14 (2725.57)	< 0.001
Pre - operation -After 24 hours	-4656.43	-3509.28	-4082.85 (3432.47)	< 0.001
Pre - operation - After 48 hours	-3893.25	-2828.74	-3361.00 (3185.20)	< 0.001
ICU entrance - After 24 hours	-2447.15	-1438.27	-1942.71 (3018.77)	< 0.001
ICU entrance - After 48 hours	-1748.54	-693.16	-1220.85 (3157.88)	< 0.001
After 24 hours - After 48 hours	292.79	1150.92	721.85 (2567.69)	0.001

Abbreviations: WBC, white blood cell; CI; confidence interval; ICU, intensive care unit.
[a]Table represents the statistical significance of increase between WBC measurement in first 24 hours and then the decrease from the 24 hours measurement and 48 hours measurement.
[b]Values are Mean (Standard Deviation).
[c]P value smaller than 0.05 is statistically meaningful.

The value of WBC for diagnosis of pneumonia is more than 12000 /mm³ ([8]). Post - operation WBC reference intervals, which were defined during the study, were all higher than the WBC normal ranges. The situation continues for at least 48 hours after the operation therefore, we recommend that the routine range of the WBC count in general population should not be considered as a reliable criterion to the diagnosis of infections and adjusted WBC values should be replaced in assessments.

Furthermore, the diagnostic guidelines should be adjusted to replace the corrected reference interval for individual groups of patients.

4.1. Limitations

This study was held in one particular ethnic group in one medical centre with particular medical protocols. By changing the clinical approaches and management of patients, some differences are expected in other future determination of reference interval. However, as reported before in other studies we should expect a significant difference in general population values. Similar studies should be held in various centers to practically use specialized values in clinical assessment.

References

1. Ascione R, Lloyd CT, Underwood MJ, Lotto AA, Pitsis AA, Angelini GD. Inflammatory response after coronary revascularization with or without cardiopulmonary bypass. *Ann Thorac Surg*. 2000;**69**(4):1198–204. [PubMed: 10800819].

2. Mazandarani M, Yousefshahi F, Abdollahi M, Hamishehkar H, Barkhordari K, Boroomand MA, et al. Comparison of hypertonic saline versus normal saline on cytokine profile during CABG. *Daru*. 2012;**20**(1):49. doi: 10.1186/2008-2231-20-49. [PubMed: 23351427]. [PubMed Central: PMC3555740].

3. Rothenburger M, Trosch F, Markewitz A, Berendes E, Schmid C, Scheld H, et al. Leukocyte activation and phagocytic activity in cardiac surgery and infection. *Cardiovasc Surg*. 2002;**10**(5):470–5. [PubMed: 12379405].

4. Yousefshahi F, Bashirzadeh M, Abdollahi M, Mojtahedzadeh M, Salehiomran A, Jalali A, et al. Effect of Hypertonic Saline Infusion versus Normal Saline on Serum NGAL and Cystatin C Levels in Patients Undergoing Coronary Artery Bypass Graft. *J Tehran Heart Cent*. 2013;**8**(1):21–7. [PubMed: 23646044]. [PubMed Central: PMC3587670].

5. Butler J, Rocker GM, Westaby S. Inflammatory response to cardiopulmonary bypass. *Ann Thorac Surg*. 1993;**55**(2):552–9. doi: 10.1016/0003-4975(93)91048-r.

6. Gasz B, Benko L, Jancso G, Lantos J, Szanto Z, Alotti N, et al. Comparison of inflammatory response following coronary revascularization with or without cardiopulmonary bypass. *Exp Clin Cardiol*. 2004;**9**(1):26–30. [PubMed: 19641693]. [PubMed Central: PMC2716259].

7. Klompas M. Does this patient have ventilator-associated pneumonia? *JAMA*. 2007;**297**(14):1583–93. doi: 10.1001/jama.297.14.1583. [PubMed: 17426278].

8. Centers for Disease Control and Prevention. *Guideline and Procedures for monitoring Ventilator Associated Pneumonia: Ventilator-Associated Pneumonia (VAP) Event*. 2012.

9. Yousefshahi F, Azimpour K, Boroumand MA, Najafi M, Barkhordari K, Vaezi M, et al. Can a new antiseptic agent reduce the bacterial colonization rate of central venous lines in post-cardiac surgery patients? *J Tehran Heart Cent*. 2013;**8**(2):70–5. [PubMed: 23967028]. [PubMed Central: PMC3740112].

10. Koenig SM, Truwit JD. Ventilator-associated pneumonia: diagnosis, treatment, and prevention. *Clin Microbiol Rev*. 2006;**19**(4):637–57. doi: 10.1128/CMR.00051-05. [PubMed: 17041138]. [PubMed Central: PMC1592694].

11. Chastre J, Fagon JY. Ventilator-associated pneumonia. *Am J Respir Crit Care Med*. 2002;**165**(7):867–903. doi: 10.1164/ajrccm.165.7.2105078. [PubMed: 11934711].

12. Barbier F, Andremont A, Wolff M, Bouadma L. Hospital-acquired pneumonia and ventilator-associated pneumonia: recent advances in epidemiology and management. *Curr Opin Pulm Med*. 2013;**19**(3):216–28. doi: 10.1097/MCP.0b013e32835f27be. [PubMed: 23524477].

13. Alvarez-Lerma F, Palomar M, Olaechea P, Otal JJ, Insausti J, Cerda E. [National Study of Control of Nosocomial Infection in Intensive Care Units. Evolutive report of the years 2003-2005]. *Medicina intensiva*. 2007;**31**(1):6–17. Spain. doi: 10.1016/S0210-5691(07)74764-2.

14. Li LY, Wang SQ. Economic effects of nosocomial infections in cardiac surgery. *J Hosp Infect*. 1990;**16**(4):339–41. [PubMed: 1980506].

15. Carrel T, Schmid ER, von Segesser L, Vogt M, Turina M. Preoperative assessment of the likelihood of infection of the lower respiratory tract after cardiac surgery. *Thorac Cardiovasc Surg*. 1991;**39**(2):85–8. doi: 10.1055/s-2007-1013938. [PubMed: 1877058].

16. *Pneumonia (Ventilator-associated [VAP] and non-ventilator-associated Pneumonia [PNEU]) Event*. 2018, [cited January]. Available from: https://www.cdc.gov/nhsn/pdfs/pscmanual/6pscvapcurrent.pdf.

17. Baghban M, Paknejad O, Yousefshahi F, Gohari Moghadam K, Bina P, Samimi Sadeh S. Hospital-acquired pneumonia in patients undergoing coronary artery bypass graft; comparison of the center for disease control clinical criteria with physicians' judgment. *Anesth Pain Med*. 2014;**4**(3). e20733. doi: 10.5812/aapm.20733. [PubMed: 25289379]. [PubMed Central: PMC4183076].

18. Vakili M, Shirani S, Paknejad O, Yousefshahi F. Acute Respiratory Distress Syndrome diagnosis after coronary artery bypass: comparison between diagnostic criteria and clinical picture. *Acta Med Iran*. 2015;**53**(1):51–6. [PubMed: 25597606].

19. Yousefshahi F, Fakhre Yasseri AM, Barkhordari K, Amini M, Salehi Omran A, Rezaei Hemami M, et al. Incidence and complications of acute kidney injury following coronary artery bypass graft: a retrospective cohort study. *Iran J Kidney Dis*. 2015;**9**(2):113–8. [PubMed: 25851289].

20. Horowitz GL. *Defining, establishing, and verifying reference intervals in the clinical laboratory: Approved guideline - Third Edition*. Clinical and Laboratory Standards Institute; 2008. Report No.: Third Edition.

21. Abdelhadi RH, Gurm HS, Van Wagoner DR, Chung MK. Relation of an exaggerated rise in white blood cells after coronary bypass or cardiac valve surgery to development of atrial fibrillation postoperatively. *Am J Cardiol*. 2004;**93**(9):1176–8. doi: 10.1016/j.amjcard.2004.01.053. [PubMed: 15110218].

22. Blum A, Massachi R, Miller H. The predictive value of white blood cell count on the success of primary percutaneous intervention of the left anterior descending artery in patients admitted with acute anterior wall myocardial infarction. *Eur J Intern Med*. 2004;**15**(3):176–80. doi: 10.1016/j.ejim.2004.01.019. [PubMed: 15245721].

23. Yousefshahi F, Barkhordari K, Movafegh A, Tavakoli V, Paknejad O, Bina P, et al. A New Method for Extubation: Comparison between Conventional and New Methods. *J Tehran Heart Cent*. 2012;**7**(3):121–7. [PubMed: 23304181]. [PubMed Central: PMC3524325].

24. Korolov Y, Lamelas P, Espinoza J, Benzadon M, Vrancic M, Piccinini F, et al. Impact of Readmissions on Long-term Mortality of Patients Undergoing Cardiac Surgery. *Argentine J Cardiol*. 2018;**85**(4):340–5.

25. Rostami M, Mirmohammadsadeghi M, Zohrenia H. Evaluating the frequency of postoperative Fever in patients with coronary artery bypass surgey. *ARYA Atheroscler*. 2011;**7**(3):119–23. [PubMed: 22577458]. [PubMed Central: PMC3347853].

26. Nemeth E, Vig K, Racz K, Koritsanszky KB, Ronkay KI, Hamvas FP, et al. Influence of the postoperative inflammatory response on cognitive decline in elderly patients undergoing on-pump cardiac surgery: a controlled, prospective observational study. *BMC Anesthesiol*. 2017;**17**(1):113. doi: 10.1186/s12871-017-0408-1. [PubMed: 28851286]. [PubMed Central: PMC5576316].

27. Gokalp O, Yesilkaya NK, Bozok S, Besir Y, Iner H, Durmaz H, et al. Effects of age on systemic inflamatory response syndrome and results of coronary bypass surgery. *Cardiovasc J Afr*. 2018;**29**(1):22–5. doi: 10.5830/CVJA-2017-030. [PubMed: 28556849].

28. Pardeshi SR, Mandke AN, Mandke NV. Suppression of the inflammatory response to cardiopulmonary bypass. *Ann Card Anaesth*. 1998;**1**(2):41–8. [PubMed: 17846465].

29. Vincent JL, Bihari DJ, Suter PM, Bruining HA, White J, Nicolas-Chanoin MH, et al. The prevalence of nosocomial infection in intensive care units in Europe. Results of the European Prevalence of Infection in Intensive Care (EPIC) Study. EPIC International Advisory Committee. *JAMA*. 1995;**274**(8):639–44. [PubMed: 7637145].