Does Obesity Predict Postoperative Mediastinitis After Cardiac Surgery? A Systematic Review and Meta-analysis

Obezite Kalp Cerrahisinden Sonra Postoperatif Mediastiniti Öngördürebilir mi? Sistematik Derleme ve Metaanaliz

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ABSTRACT Objective: Mediastinitis following cardiac surgery, is an important complication. Many of risk factors that may cause mediastinitis analysed in three groups as preoperative, intraoperative and postoperative variables. The preoperative risk factors are especially important to predict development of mediastinitis before surgery and also to plan the preventive interventions. In this meta analysis, we aimed to analyze whether preoperative obesity was a risk factor for development of mediastinitis after open cardiac surgery or not. **Material and Methods:** The literature screening was performed at Pubmed, Ovid and Science direct databases without date limitation. The results of trials were evaluated with random or fixed effect model according to the heterogenity. The statistical evaluation was performed by using Comprehensive Meta Analysis version 2 programme. **Results:** Records identified through database searching were 5009 and records identified through database searching with filter were 999. After duplicates were removed, 374 records remained. Unrelated records (n=255) were excluded after screening. Full-text of 119 articles were assessed for eligibility and 97 of them were excluded because of absence of detailed data. Twenty-two articles were included to meta-analysis which contain 86367 patients and inclusion criteria. The rate of mediastinitis was 2% (1798 of 86367). Effect size was observed as heterogeneous (Q:50, df(Q):21, p:0.00, I2:58.06%). Results of analysis according to random effect model were (OR 2.33, 95% CI 1.91-2.83, Z:8.4 and p:0.00 (p<0.05). **Conclusion:** The results of quantitative analysis showed that the preoperative obesity can predict development of mediastinitis after cardiac surgery. However, further randomised controlled trials are needed for analysis to decrease the heterogeneity.

Key Words: Cardiac surgical procedures; mediastinitis; obesity

ÖZET Amaç: Kalp cerrahisinden sonra gelişen mediastinit, önemli bir komplikasyondur. Mediastinite neden olan risk etkenleri preoperatif, intraoperatif ve postoperatif olmak üzere üç grupta analiz edilebilir. Preoperatif risk etkenleri özellikle mediastinit gelişimini cerrahiden önce belirlemek ve önleyici müdahaleleri planlamak için önemlidir. Bu meta analizde, preoperatif obezitenin açık kalp cerrahisinden sonra mediastinit gelişimi için risk etkeni olup olmadığını analiz etmeyi amaçladık. **Gereç ve Yöntemler:** Literatür taraması, tarih sınırlaması olmadan Pubmed, Ovid ve Science direct veritabanlarında uygulandı. Araştırmaların bulguları, heterojenite varlığına göre random ya da sabit etki modeli ile değerlendirildi. İstatistiksel değerlendirme, Comprehensive Meta Analysis version 2 programı kullanılarak uygulandı. **Bulgular:** Veritabanı elektronik taramasından elde edilen raporlar 5009 ve veritabanı taraması filtresi ile elde edilen raporlar 999 idi. Yenileyen makaleler elendikten sonra 374 rapor kaldı. İncelemeden sonra ilgisiz raporlar (n=255) dışlandı. 119 makalenin tam metinleri uygunluk için değerlendirildi ve 97'si ayrıntılı verilerin yokluğundan dolayı hariç tutuldu. 86367 hastayı içeren ve dahil etme kriterlerini kapsayan yirmi iki makale meta analize dahil edildi. Mediastinit oranı %2 idi (1798/86367). Etki büyüklüklerinin heterojen olduğu gözlendi (Q:50, df(Q):21, p:0,00, I2:%58,06). Analiz sonucu random etki modeline gore OR:2,33, %95 GA 1,91-2,83, Z:8,4 and p:0,00 idi (p<0,05). **Sonuç:** Kantitatif analiz sonucu, obezitenin kalp cerrahisinden sonra mediastinit gelişimini önceden tahmin ettirebileceğini göstermiştir. Fakat, heterojenitenin azaltılmak amacıyla analiz için randomize kontrollü araştırmalara ihtiyaç vardır.

Anahtar Kelimeler: Kardiyak cerrahi işlemler; mediastinit; obezite

Mediastinitis following cardiac surgery, develops at a rate between 0.8% and 1.3% in the larger observational studies.[1-4] Many of risk factors that may cause mediastinitis analysed in three groups as preoperative, intraoperative and postoperative variables. The preoperative risk factors are especially important to predict development of mediastinitis before surgery and also to plan the preventive interventions. Obesity (body mass index-BMI>30 kg/m^2) is one of these risk factors that can affect the postoperative morbidity. In multivariate analysis, obesity has been determined as a predictor of mediastinitis.[2,3] However, Ashley et al. observed obesity as a risk factor for mediastinitis due to methicillin-susceptible *S. aureus* (OR:2.49, %CI:1.25-4.96, p:0.01) but not due to methicillin-resistant *Staphylococcus aureus*.[5]

In this meta-analysis, we aimed to investigate the role of obesity on development of mediastinitis after open cardiac surgery.

MATERIAL AND METHODS

SEARCH STRATEGY

We performed the database searching and we controlled the article in accordance with the guideline of *Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA).*[6] We applied the electronic database search to determine whether obesity could predict development of mediastinitis after cardiac surgery or not. Two authors (S.Ö and İ.Ö.) searched database until 15.05.2014. No limitation was used for date. Pubmed, Ovid and Science direct were used as databases.

The keywords or combinations of them (*cardiac surgery, heart surgery, valve surgery, coronary artery bypass grafting, deep sternal wound infection, mediastinitis, obesity*) were used for searching. Searching was limited with English and the articles in other languages were excluded. The methods of studies were limited with '*clinical trial, comparative study, multicenter study, observational study, randomized controlled trial, controlled clinical trial and evaluation studies*'.

SELECTION OF STUDIES

The studies, regardless of sample size, were included retrospective or prospective clinical studies. Inclusion criteria were: clinical study, open cardiac surgery with off pump or extracorporeal circulation, article in English. Exclusion criteria were: experimental studies, articles in non-english language and non-cardiac surgery. The articles, associated with the issue our review but not contain the knowledge about the rate of mediastinitis according to preoperative obesity, were also excluded. Articles contain data with figures not numerical values were excluded.

DATA EXTRACTION

Two reviewers (S.Ö. and İ.Ö.) independently extracted data from relevant studies. We extracted publication information (first author's name, publication year, patient population, type of surgery), characteristics of participants (sample size, type of study methods) and outcome information (mediastinitis rate, number of patients with obesity and control cases). Disagreement was resolved by consensus with the third reviewer (S.I.). The number of patients with obesity according to mediastinitis and non-mediastinitis were recorded as data.

STATISTICAL ANALYSIS

The meta-analysis programme, Comprehensive Meta Analysis (CMA) Version 2.0 (Biostat, Englewood, New Jersey, USA), was used for statistical analysis. The odds ratio (OR) and 95% confidence interval (CI) was used for analysis. The heterogeneity was evaluated with the statistics of I^2. Heterogeneity was accepted as significant if $I^2 > 25\%$ and heterogeneity was evaluated with the analysis of subgroups and moderators. Heterogeneity was determined as low ($25\% < I^2 < 50\%$), moderate ($50\% < I^2 < 75\%$) or high ($I^2 > 75\%$). Meta-analysis was applied by using fixed or random effect models. We performed fixed effect model in the absence of heterogeneity ($I^2 < 25\%$) and random effect model in presence of heterogeneity ($I^2 > 25\%$). The overall effect was analysed with Z score. Potential publication bias was evaluated with funnel plot and Begg test.

RESULTS

Flow diaphragm of database searching was shown in Figure 1. Records identified through database searching were 6057 and records identified through database searching with filter were 999. After duplicates were removed, 374 records remained. Unrelated records (n=255) were excluded after screening. Full-text of 119 articles was assessed for eligibility and 97 of them were excluded because of absence of detailed data. 22 articles were included to quantitative synthesis.[2-5,7-24] Demographical features of studies were summarized in Table 1. The ratio of development of mediastinitis was 2% (1798 of 86367). Total of patients with obesity was 18310 (21.21%, 18310/86367) while total of patients without obesity was 68032 (78.79%, 68032/86367). And ratio of obese patients with mediastinitis was 45% (809/1798) while ratio of non-obese patients with mediastinitis was 55% (989/1798).
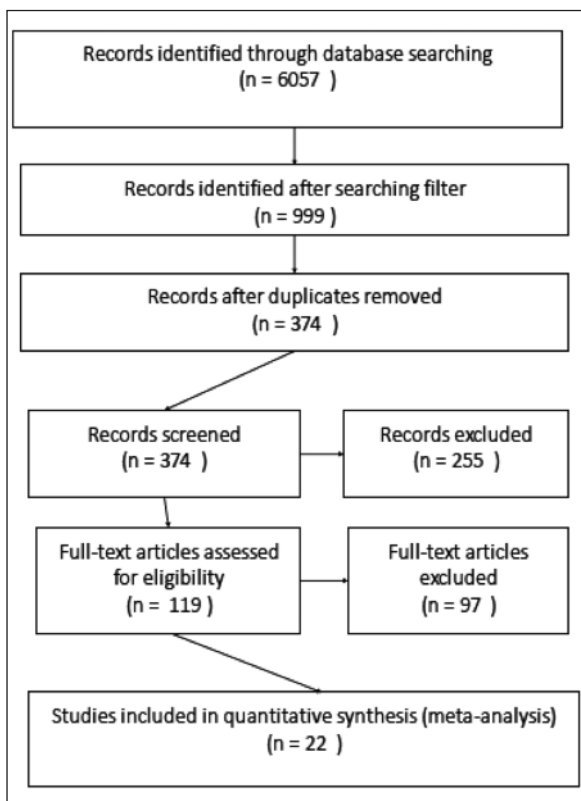
The result of the analysis of 22 studies was OR 2.33, 95% CI 1.91-2.83, Z:8.4 and p:0.00 (p<0.05). The result favours non-obesity. Baillot et al.'s (8.5%) had the largest effect weight and Sa et al.'s study (1.32%) had the smallest effect weight according to random effect model.[3,8] The effect weight of trials were not homogenous (Q:50, df(Q):21, p:0.00, I^2:58.06%). Heterogeneity was evaluated with moderators (study design, type of procedures and presence of difference according to systematical diseases). Heterogeneity reduced with presence of difference according to systematical diseases (Table 2). The results of analysis were summarized in Figure 2.

The result of evaluation of publication bias was not significant according to Begg test (tau^2=0,1). The number of possible articles that escape notice during database search was 967 (classic fail-safe N), but we could not get further articles with appropriate data. The funnel plot was shown in Figure 3.

DISCUSSION

Obesity defined as BMI>30 kg/m^2 is a common medical problem especially in recent years. Approximately more than 25-30% of American and European people are obese.[25] Rate of obesity in open cardiac surgical patients is between 0.2% and 23%.[2,12] Therefore, it is a serious possible cause for morbidity and mortality in that surgical population.

In relation to postoperative mediastinitis, obesity is important in two main issues. First; obesity is generally a risk factor for infections. And second; obesity is associated with other systematical diseases such as diabetes mellitus, hypertension, cardiac events and dyslipidemia which can be predisposing factors of mediastinitis.

Obesity is accepted as a predisposing factor for infections in different organs or systems. There are many possible mechanisms which are associated with respiratory tract, skin and bone tissues, immune response, obesity related co-morbidity and pharmacological changes.[26]

Myles et al. determined obesity as an independent risk factor for non-cardiac surgery.[27] That

FIGURE 1: Flow diaphragm of database searching.

TABLE 1: Studies included to analysis.					
References	Surgical procedure	Design of study	Obese patients (n)	Non-obese patietns (n)	Levels of evidence
Abboud et al.[12]	Combined	Retrospective	27	90	3b
Antunes et al.[21]	CABG	Prospective	401	2111	2b
Ashley et al.[5]	Combined	Prospective	125	98	2b
Baillot et al.[3]	Combined	Combined	5856	17643	3b
Braxton et al.[4]	CABG	Retrospective	4660	10746	3b
Colombier et al.[19]	Combined	Retrospective	73	149	3b
Dial et al.[8]	Combined	Retrospective	15	29	3b
Elenbaas et al.[2]	CABG	Prospective	320	11428	2b
Filsoufi et al.[23]	CABG	Retrospective	1250	4548	3b
Floros et al.[17]	Combined	Prospective	1865	3784	2b
Ghotaslou et al.[15]	Combined	Retrospective	622	1205	3b
Lopez-Gude et al.[22]	Combined	Prospective	80	409	2b
Milano et al.[18]	CABG	Prospective	201	6258	2b
Parissis et al.[20]	Combined	Prospective	1694	2254	2b
Careaga et al.[16]	Combined	Retrospective	97	72	3b
Ridderstolpe et al.[24]	Combined	Retrospective	457	2551	3b
Rosmarakis et al.[11]	Combined	Prospective	77	283	2b
Sa et al.[14]	CABG	Retrospective	83	445	3b
Sa et al.[7]	CABG	Retrospective	25	132	3b
San Juan et al.[9]	Combined	Prospective	13	55	2b
Tiveron et al.[13]	Combined	Prospective	254	2514	2b
Wouters et al.[10]	CABG	Retrospective	140	1228	3b

CABG: Coronary artery bypass grafting.

TABLE 2: Subgroup analysis.					
Subgroup	Variable	No. of study	OR(95%CI)	p heterogeneity	I² (%)
Study design	Prospective	10	2.54 (2.0-3.1)	0.001	67.8
	Retrospective	11	2.20 (1.8-2.5)	0.02	51.9
	Both	1	2.41 (1.8-3.1)	1.0	0.0
Type of procedure	CABG	8	2.99 (2.1-4.0)	0.04	52.2
	Combined	14	2.00 (1.5-2.5)	0.006	55.8
Difference for diseases*	Yes	14	2.54 (2.0-3.1)	0.001	62.2
	No	8	1.71 (1.1-2.6)	0.17	31.1

Difference for diseases*= Significant differences between the groups with or without mediastinitis according to systemical diseases.

result was not changed despite both elective or urgent surgery and appropriate antimicrobial prophylaxis. Infection in skin or bone tissues is due to impaired micro- and macrocirculation and decrease of wound healing.[28]

The second important point for obesity is co-existing diseases. Increasing BMI may increase risk of chronic diseases such as heart disease, cancer, stroke, hypertension, dyslipidemia and diabetes mellitus.[29] Diabetes mellitus and aterosclerosis may predispose infections in obesity.[26] At this point co-existing diseases and medical conditions associated with obesity is more important in cardiac surgical patients. Because they are more likely to have those diseases. And those conditions can independently cause postoperative mediastinitis after cardiac sur-
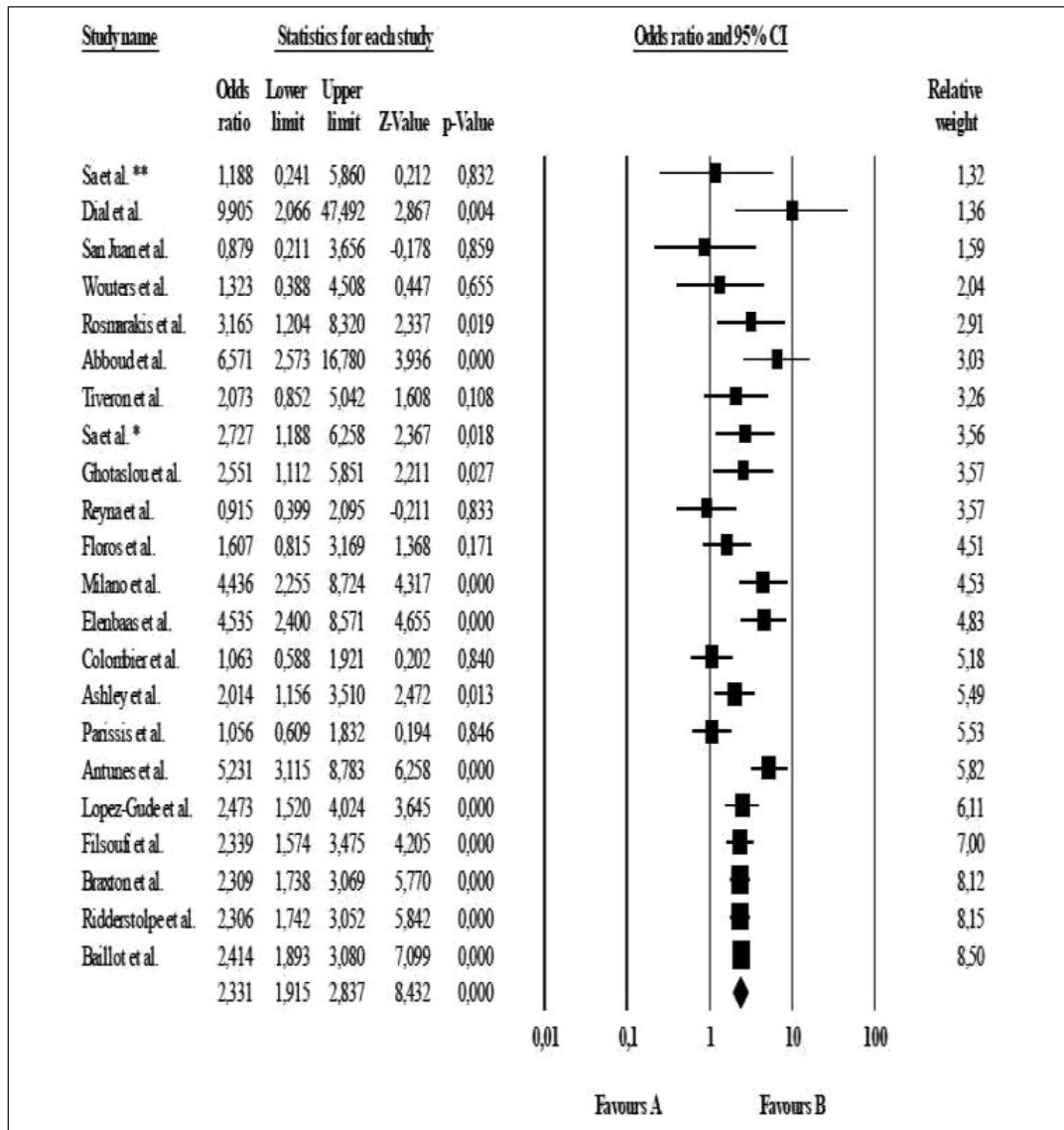
Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Odds ratio and 95% CI	Relative weight
Sa et al. **	1,188	0,241	5,860	0,212	0,832		1,32
Dial et al.	9,905	2,066	47,492	2,867	0,004		1,36
San Juan et al.	0,879	0,211	3,656	-0,178	0,859		1,59
Wouters et al.	1,323	0,388	4,508	0,447	0,655		2,04
Rosmarakis et al.	3,165	1,204	8,320	2,337	0,019		2,91
Abboud et al.	6,571	2,573	16,780	3,936	0,000		3,03
Tiveron et al.	2,073	0,852	5,042	1,608	0,108		3,26
Sa et al. *	2,727	1,188	6,258	2,367	0,018		3,56
Ghotaslou et al.	2,551	1,112	5,851	2,211	0,027		3,57
Reyna et al.	0,915	0,399	2,095	-0,211	0,833		3,57
Floros et al.	1,607	0,815	3,169	1,368	0,171		4,51
Milano et al.	4,436	2,255	8,724	4,317	0,000		4,53
Elenbaas et al.	4,535	2,400	8,571	4,655	0,000		4,83
Colombier et al.	1,063	0,588	1,921	0,202	0,840		5,18
Ashley et al.	2,014	1,156	3,510	2,472	0,013		5,49
Parissis et al.	1,056	0,609	1,832	0,194	0,846		5,53
Antunes et al.	5,231	3,115	8,783	6,258	0,000		5,82
Lopez-Gude et al.	2,473	1,520	4,024	3,645	0,000		6,11
Filsoufi et al.	2,339	1,574	3,475	4,205	0,000		7,00
Braxton et al.	2,309	1,738	3,069	5,770	0,000		8,12
Ridderstolpe et al.	2,306	1,742	3,052	5,842	0,000		8,15
Baillot et al.	2,414	1,893	3,080	7,099	0,000		8,50
	2,331	1,915	2,837	8,432	0,000		

FIGURE 2: Results of analysis. Favours A: Obesity, Favours B: Non-Obesity.

gery. Most of them were analysed in the studies according to univariate or multivariate analysis. While diabetes mellitus, hypertension, renal insuffiency, peripheral vascular disease, atrial fibrillation were determined as risk factors in univariate analysis diabetes mellitus, peripheral vascular disease, atrial fibrillation, chronic obstructive pulmonary disease and renal insuffiency were found independent risk factors for mediastinitis in multivariate analysis.[2,5,7,10,13,19,20,22-24]

The studies focused on mediastinitis risk factors are case-control or cohort trials. Because of
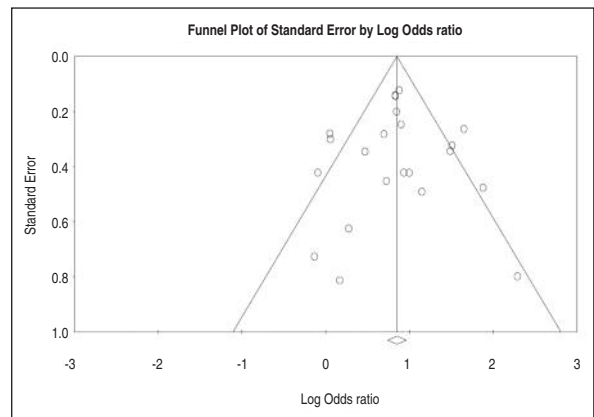

FIGURE 3: Funnel plot of publication bias.

that there are significant differences between groups with mediastinitis and controls in relation to co-existing diseases. In 8 of 22 studies, authors did not find significant differences between groups.[7-11,13,17,19] When we take into consideration the differences between the groups in relation to systemic diseases, we performed a subgroups analysis. Although the heterogeneity has decreased (I^2: 31.1%), nor presence of heterogeneity neither the result of analysis had not changed.

LIMITATIONS

The main limitation of our analysis was absence of randomized controlled trials. Our analysis was consist of prospective cohort or retrospective case-control trials. Second limitation was the data of trials were consist of both off- and on-pump

surgery for many of the articles except reference 11 (it was done for only off-pump). Becasue of that reason we could not discuss the effect of obesity on postoperative mediastinitis according to off- or on-pump techniques. In our opinion, possibility of changes of result by prospective randomized controlled trials is important for higher level of evidence.

CONCLUSION

In conclusion, we found that obesity was a predictor for development of postoperative mediastinitis after open cardiac procedures. However, further studies, especially larger randomized controlled, are needed to confirm this result at level of evidence 1.

REFERENCES

1. Robinson PJ, Billah B, Leder K, Reid CM; ASCTS Database Committee. Factors associated with deep sternal wound infection and haemorrhage following cardiac surgery in Victoria. Interact Cardiovasc Thorac Surg 2007; 6(2):167-71.

2. Elenbaas TW, Soliman Hamad MA, Schönberger JP, Martens EJ, van Zundert AA, van Straten AH. Preoperative atrial fibrillation and elevated C-reactive protein levels as predictors of mediastinitis after coronary artery bypass grafting. Ann Thorac Surg 2010;89(3): 704-9.

3. Baillot R, Cloutier D, Montalin L, Côté L, Lellouche F, Houde C, et al. Impact of deep sternal wound infection management with vacuum-assisted closure therapy followed by sternal osteosynthesis: a 15-year review of 23,499 sternotomies. Eur J Cardiothorac Surg 2010;37(4):880-7.

4. Braxton JH, Marrin CA, McGrath PD, Ross CS, Morton JR, Norotsky M, et al.; Northern New England Cardiovascular Disease Study Group. Mediastinitis and long-term survival after coronary artery bypass graft surgery. Ann Thorac Surg 2000;70(6):2004-7.

5. Dodds Ashley ES, Carroll DN, Engemann JJ, Harris AD, Fowler VG Jr, Sexton DJ, et al. Risk factors for postoperative mediastinitis due to methicillin-resistant Staphylococcus aureus. Clin Infect Dis 2004;38(11):1555-60.

6. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the

PRISMA statement. BMJ 2009 Jul 21;339:b2535. doi: 10.1136/bmj.b2535.

7. Sá MP, Soares EF, Santos CA, Figueiredo OJ, Lima RO, Escobar RR, et al. Skeletonized left internal thoracic artery is associated with lower rates of mediastinitis in diabetic patients. Rev Bras Cir Cardiovasc 2011;26(2):183-9.

8. Dial S, Nguyen D, Menzies D. Autotransfusion of shed mediastinal blood: a risk factor for mediastinitis after cardiac surgery? Results of a cluster investigation. Chest 2003;124(5):1847-51.

9. San Juan R, Chaves F, López Gude MJ, Díaz-Pedroche C, Otero J, Cortina Romero JM, et al. Staphylococcus aureus poststernotomy mediastinitis: description of two distinct acquisition pathways with different potential preventive approaches. J Thorac Cardiovasc Surg 2007;134(3):670-6.

10. Wouters R, Wellens F, Vanermen H, De Geest R, Degrieck I, De Meerleer F. Sternitis and mediastinitis after coronary artery bypass grafting. Analysis of risk factors. Tex Heart Inst J 1994;21(3):183-8.

11. Rosmarakis ES, Prapas SN, Rellos K, Michalopoulos A, Samonis G, Falagas ME. Nosocomial infections after off-pump coronary artery bypass surgery: frequency, characteristics, and risk factors. Interact Cardiovasc Thorac Surg 2007;6(6):759-67.

12. Abboud CS, Wey SB, Baltar VT. Risk factors for mediastinitis after cardiac surgery. Ann Thorac Surg 2004;77(2):676-83.

13. Tiveron MG, Fiorelli AI, Mota EM, Mejia OA, Brandão CM, Dallan LA, et al. Preoperative risk factors for mediastinitis after cardiac surgery: analysis of 2768 patients. Rev Bras Cir Cardiovasc 2012;27(2):203-10.

14. Sá MP, Soares EF, Santos CA, Figueiredo OJ, Lima RO, Escobar RR, et al. Risk factors for mediastinitis after coronary artery bypass grafting surgery. Rev Bras Cir Cardiovasc 2011;26(1):27-35.

15. Ghotaslou R, Yagoubi AR, Khalili AA, Mahmodian R. Mediastinitis after cardiac surgery in Madani Heart Center, Tabriz, Iran. Jpn J Infect Dis 2008;61(4):318-20.

16. Careaga Reyna G, Aguirre Baca GG, Medina Concebida LE, Borrayo Sánchez G, Prado Villegas G, Argüero Sánchez R. [Risk factors for mediastinitis and sternal dehiscence after cardiac surgery]. Rev Esp Cardiol 2006;59(2):130-5.

17. Floros P, Sawhney R, Vrtik M, Hinton-Bayre A, Weimers P, Senewiratne S, et al. Risk factors and management approach for deep sternal wound infection after cardiac surgery at a tertiary medical centre. Heart Lung Circ 2011;20(11):712-7.

18. Milano CA, Kesler K, Archibald N, Sexton DJ, Jones RH. Mediastinitis after coronary artery bypass graft surgery. Risk factors and long-term survival. Circulation 1995;92(8):2245-51.

19. Colombier S, Kessler U, Ferrari E, von Segesser LK, Berdajs DA. Influence of deep sternal wound infection on long-term survival after cardiac surgery. Med Sci Monit 2013;19:668-73.

20. Parissis H, Al-Alao B, Soo A, Orr D, Young V. Risk analysis and outcome of mediastinal wound and deep mediastinal wound infections with specific emphasis to omental transposition. J Cardiothorac Surg 2011 Sep 19;6:111. doi: 10.1186/1749-8090-6-111.

21. Antunes PE, Bernardo JE, Eugénio L, de Oliveira JF, Antunes MJ. Mediastinitis after aorto-coronary bypass surgery. Eur J Cardiothorac Surg 1997;12(3):443-9.

22. López Gude MJ, San Juan R, Aguado JM, Maroto L, López-Medrano F, Cortina Romero JM, et al. Case-control study of risk factors for mediastinitis after cardiovascular surgery. Infect Control Hosp Epidemiol 2006;27(12):1397-400.

23. Filsoufi F, Castillo JG, Rahmanian PB, Broumand SR, Silvay G, Carpentier A, et al. Epidemiology of deep sternal wound infection in cardiac surgery. J Cardiothorac Vasc Anesth 2009;23(4):488-94.

24. Ridderstolpe L, Gill H, Granfeldt H, Ahlfeldt H, Rutberg H. Superficial and deep sternal wound complications: incidence, risk factors and mortality. Eur J Cardiothorac Surg 2001;20(6):1168-75.

25. Berghöfer A, Pischon T, Reinhold T, Apovian CM, Sharma AM, Willich SN. Obesity prevalence from a European perspective: a systematic review. BMC Public Health 2008 Jun 5;8:200. doi: 10.1186/1471-2458-8-200.

26. Huttunen R, Syrjänen J. Obesity and the risk and outcome of infection. Int J Obes (Lond) 2013;37(3):333-40.

27. Myles TD, Gooch J, Santolaya J. Obesity as an independent risk factor for infectious morbidity in patients who undergo cesarean delivery. Obstet Gynecol 2002;100(5 Pt 1):959-64.

28. Yosipovitch G, DeVore A, Dawn A. Obesity and the skin: skin physiology and skin manifestations of obesity. J Am Acad Dermatol 2007;56(6):901-16; quiz 917-20.

29. Nguyen NT, Magno CP, Lane KT, Hinojosa MW, Lane JS. Association of hypertension, diabetes, dyslipidemia, and metabolic syndrome with obesity: findings from the National Health and Nutrition Examination Survey, 1999 to 2004. J Am Coll Surg 2008;207(6):928-34.