

Dear editor,

First and foremost, I thank the reviewers for their time, valuable insights, and constructive comments.

We marked our answers in **red** and the parts we added to the text in **green**.

Response to Reviewer #1:

Their results robustly confirm that the jugular vein route is safer than the subclavian vein approach for central venous port implantation. It is interesting for others, however, something needs be revised, such as language, table, it is not clear to be understood.

Can not agree more, being easy to understand is really important for an article and similarly, tables should be easily interpretable.

Many thanks for this warning we tried to revise the manuscript and the tables in order to make them more apprehensible.

Responses to Reviewer #2:

1. We do recognize that jugular veins route seems to be a safer alternative to the subclavian vein approach with lower risks of total major mechanical complications, according to a recent meta-analysis which include twelve studies including 3905 patients published between 2008 and 2015. Then, the innovating points and the purposes of current study need to be better stated in the introduction section. Reference: Wu S, Huang J, Jiang Z, et al. Internal jugular vein versus subclavian vein as the percutaneous insertion site for totally implantable venous access devices: a meta-analysis of comparative studies. BMC Cancer. 2016;16(1):747. Published 2016 Sep 22. doi:10.1186/s12885-016-2791-2

Thank you for sharing this critical meta-analysis. We cited this relevant and crucial study and innovative points, and the purposes of our study were tried to be more clearly emphasized in the introduction section.

“Introduction: In a meta-analysis comparing these two leading options, it was shown that there was no difference between the two methods in terms of catheter-related infection and thrombotic events (wu20). It was observed that catheter dislocation and malfunction were more in the subclavian route, but there was no difference between the groups regarding port fracture. As a result of this meta-analysis, in which 12 studies and 3905 patients were evaluated, it was concluded that the internal jugular vein is a safer route than the subclavian vein, and significant mechanical problems such as dislocation and malfunction are less common.

In this study, we retrospectively evaluated 200 patients with venous ports implanted through the jugular or subclavian veins. Besides the demographic characteristics of patients, the main focus of this study was to compare the complication risks of these methods to find out the method of choice for central venous port implantation.

Discussion: In the meta-analysis of Wu et al., it is stated that ...”

2. Were the operation of these two methods performed by doctor with same operative experience? I think this need to be clearly stated in the method section to reduce the selection bias.

Thank you for reminding us of this important information we missed. We have added this to the “MATERIALS AND METHODS / Study design” section.

“All procedures were performed by two experienced senior surgeons of the General Surgery Department and ...”

3. Applying tests to the categorical variables is less straightforward than the authors have assumed. P-value calculated by pearson χ^2 test is not the most appropriate statistical value to use for 2x2 tables when numbers of the positive cases were too limited. For example, regarding the catheter occlusion, zero occlusion occur in Group 1, and four occlusions occur in Group 1, then the

significance should better be calculated with Fisher's exact test, and the authors will see that the p-values currently used in the paper for categorical data will all increase.

We appreciate your attention and assiduity with the statistical evaluations. We discussed your comments in detail with the statistical consultant of our study (Mr Ertan Koç). In the statistical analysis of our study, the Chi-Square test conditions were re-examined, and the conditions were met. Significances were also evaluated with Fisher's exact test, and tables are attached below*.

Considering your warning and to avoid misunderstanding, we have removed the p-value specified in the text after occlusion & infection because this p-value is the result of the analysis made to compare not only occlusions or infections but all complications.

The rate of port occlusion was found to be higher in Group 2 when compared to Group 1 patients.

The infection rate was higher in Group 2 compared to Group 1.

4. Regarding the infection, the authors claim that infection developed in 1 patient in Group 1 and 3 patients in Group 2. But the question here is: whether the infections occurred in these two groups were all catheter related. I think that's important, then one case of superficial surgical site infection should not be enrolled in the final analysis, and the statistical significance should be recalculated.

In group 1, there was a patient with pancreatic cancer, and both blood and catheter cultures revealed *Candida albicans*. For this reason, it will be appropriate to consider this catheter-related infection. In Group 2, one patient out of three infections had a superficial surgical site infection. It was resolved by local care. We realised that your warning was very accurate; we removed this patient from the complication list and revised the total number to 18, and grateful for this. However, this revision does not affect the statistical result. Corrections have also been made to the table.

5. Regarding the catheter rupture, we notice that one linear complete separation was identified in 1 patient in the group. The authors should provide additional information, including the timing between catheter fracture and angiographic intervention, the secondary injury and whether catheter occlusion have occurred before and if so, how the event were treated?

The port fracture patient had a colon cancer diagnosis. His port was inserted on July 2014. His last uneventful chemotherapy via port was on 02.07.2015. At his next scheduled chemotherapy visit (17.08.2015) responsible nurse realised that there was no blood return (she could not draw blood from the port). Chest X-ray revealed that the distal end of the catheter was broken and displaced inside the heart. The next day the distal end was removed with angiographic intervention. The proximal part was removed on the same day, and a new port was inserted from the opposite side. No data for previous catheter occlusion and timing of the angiographic intervention (next day) is inserted into the manuscript.

6. The authors give us hints that the intravascular and extravascular catheter angle above 60 degrees was the reason for the occurrence of the catheter rupture. We were cautious about this view. Could it possibly be the results of the pinch-off syndrome?

The pinch-off syndrome you mentioned about catheter breakage is, of course, a crucial factor. When we consider other factors that should be considered to prevent catheter rupture apart from this syndrome, we concluded that the intravascular and extravascular catheter angle is also critical. The risk of breakage increases when this angle is not taken care of and mainly when port catheter flushes are performed with high pressure. Considering your appropriate remark, we have added a sentence about this syndrome to the manuscript and the relevant reference.

Thus besides the pinch-off syndrome, we believe that we must also consider this angle to prevent ruptures.

7. The authors dedicate a significant portion of the discussion section about the ports washing. They advocate a longer 2-month interval for port care and washing. I think that port care and washing method should also be stated in the methodological section.

Perfect point; we inserted our protocol into the “MATERIALS AND METHODS / Follow-up” section.

According to our clinical protocol, the venous ports of the patients are evaluated and washed with 1000 U heparin every 2 mo.

8. The authors might want to provide information on the catheter-related thrombotic complications. It might be the main reason of catheter occlusion.

Thank you for this constructive comment. We elaborated on our thrombotic complications in the discussion section.

Cancer patients tend to thrombosis. In the meta-analysis of Wu et al., it is stated that flushing with heparinized fluid is the primary method in the prevention of catheter thrombosis. In patients with thrombosis, it may be necessary to remove the port if it can not be opened with conservative methods. In our study, there was no obstruction in the jugular ports. Obstruction due to thrombosis was detected in 4 patients in whom the subclavian route was used. One of them was opened by pressure washing with heparin, and the port was removed in the other three patients because thrombosis could not be opened with conservative treatment.

9. The operation process of the jugular vein puncture and port placement was too verbose, and it needs clear explanation and concise presentation.

Considering this valuable comment, we have abbreviated this section and revised it.

10. In the method section, what does this sentence mean? “Patients were hospitalized in the same-day surgery unit”, it better corrected as “Patients were hospitalized in the same day-surgery unit” ?

The sentence was revised as you suggested, thank you.

Patients were hospitalized in the same-day surgery unit.

Reviewer #3:

I have reviewed with pleasure your paper and it seems to me a good work. I have no objection or comment to it.

Thank you very much for this support for our work, which is very important to us.

Responses to Revision reviewer:

it better corrected as “Patients were hospitalized in the same day-surgery unit” . Acceptable to me.

The sentence was revised as you suggested, thank you.

Patients were hospitalized in the same-day surgery unit.

Best Regards,

Kemal Raşa

*Fisher exact test tables

Sex			Total
	Group 1	Group 2	
F	43	56	99
M	57	44	101
Total	100	100	200

Chi-Square Tests

	Value	df	Asymptotic Significance (2- sided)	Exact Sig. (2- sided)	Exact Sig. (1- sided)
Pearson Chi-Square	3,380a	1	,066		
Continuity Correctionb	2,880	1	,090		
Likelihood Ratio	3,390	1	,066		
Fisher's Exact Test				,089	,045
Linear-by-Linear Association	3,363	1	,067		
N of Valid Cases	200				

a. 0 cells (0,0%) have expected count less than 5. The minimum expected count is 49,50.

b. Computed only for a 2x2 table

Side			Total
	Group 1	Group 2	
Right	91	95	186
Left	9	5	14
Total	100	100	200

Chi-Square Tests

	Value	df	Asymptotic Significance (2- sided)	Exact Sig. (2- sided)	Exact Sig. (1- sided)
Pearson Chi-Square	1,229a	1	,268	,407	,203
Continuity Correctionb	,691	1	,406		
Likelihood Ratio	1,245	1	,265		
Fisher's Exact Test					
Linear-by-Linear Association	1,223	1	,269		
N of Valid Cases	200				

a. 0 cells (0,0%) have expected count less than 5. The minimum expected count is 7,00.

b. Computed only for a 2x2 table

Number of chemotherapy drugs			Total
	Group 1	Group 2	
1	46	41	87
2	42	41	83
3	12	18	30
Total	100	100	200

Chi-Square Tests

	Value	df	Asymptotic Significance (2- sided)
Pearson Chi-Square	1,499a	2	,473
Likelihood Ratio	1,508	2	,471
Linear-by-Linear Association	1,195	1	,274
N of Valid Cases	200		

a. 0 cells (0,0%) have expected count less than 5. The minimum expected count is 15,00.

Complications			Total
	1	2	
Absent	98	81	179
Present	2	19	21
Total	100	100	200

Chi-Square Tests

	Value	df	Asymptotic Significance (2- sided)	Exact Sig. (2- sided)	Exact Sig. (1- sided)
Pearson Chi-Square	15,376a	1	,000	,000	,000
Continuity Correctionb	13,621	1	,000		
Likelihood Ratio	17,520	1	,000		
Fisher's Exact Test					
Linear-by-Linear Association	15,300	1	,000		
N of Valid Cases	200				

a. 0 cells (0,0%) have expected count less than 5. The minimum expected count is 10,50.

b. Computed only for a 2x2 table

Crosstab

Clavien-Dindo classification	Giriş		Total
	1	2	
0	98	81	179
2	1	6	7
3	1	13	14
Total	100	100	200

Chi-Square Tests

	Value	df	Asymptotic Significance (2- sided)
Pearson Chi-Square	15,472a	2	,000
Likelihood Ratio	17,783	2	,000
Linear-by-Linear Association	15,221	1	,000
N of Valid Cases	200		

a. 2 cells (33,3%) have expected count less than 5. The minimum expected count is 3,50.