PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Patient-related factors associated with superficial surgical site infection and progression to a periprosthetic joint infection after elective primary total joint arthroplasty: a single-centre, retrospective study in Sweden
AUTHORS	Eriksson, Hannah; Lazarinis, Stergios

VERSION 1 – REVIEW

REVIEWER	Kishawi, Deena AMITA Health, Obstetrics & Gynecology
REVIEW RETURNED	31-Jan-2022

GENERAL COMMENTS	Hello! I want to first commend you on a job well done. This is a critical concern for TJA and something we hope to always address, research, and minimize for the future. There are a few things I would like to address. 1. There are some newer articles that address the rates of infection in obese patients, especially using NSQIP in the US or other similar databases worldwide. There are quite a few studies in your references that are over 10 (even 20) years old. Given the abundance of research since then, there are more relevant and clinically applicable research articles that should be referenced and included. 2. There are some speculative studies that look into rates of SSI and PJI by surgeon (attending vs resident, junior vs senior surgeon). Is this a variable you can look into? It would be worthwhile to control for variables such as this. 3. Similarly, the greater the number of people scrubbed into the surgery, I'd speculate that there would be greater rates of infection or bacterial transmission. Can you retroactively review this or at least comment on it in your manuscript? 4. There is a lot of research that shows that the time on the OR table leads to greater rates of morbiditiy and mortality - as there is more time for things to go wrong. Similarly, is this a variable you can look into and control for? I anticipate that there might be a relationship with the rates of SSI and PJI with longer surgeries. 5. Regarding age... Now, this specific variable of interest has a lot of sub-components that can reasonably contribute to greater rates of SSI and they are not addressed. As one ages, their nutritional status decreases. Typically, they are not eating as well a rounded diet as before, and their caloric intake may be above or below what is recommended. Other factors that can look at nutritional status include albumin, as this would give a good clinical picture in relation to their diet over the last few months. Also, older patients have decreased collagen and elasticity, as is natural with aging,

	and therefore have decreased wound healing complexes, which can further be a contributing factor to SSI and PJI. Please consider editing your manuscript to include these in your discussion, and if possible, retroactively comparing nutritional status. 6. As mentioned, due to the sample size, there is a greater chance for a Type II statistical error but I appreciate you addressing this early in the manuscript. Lastly, as mentioned, this was a well written and well-researched project. With only a few minor revisions and expansion regarding a few topics of interest, as listed above, it would be ready for publication.

REVIEWER	Castano-Betancourt, Martha Cecilia FMJ, Postgraduate
REVIEW RETURNED	14-Feb-2022

GENERAL COMMENTS	The authors presented a paper to identify patient-related risk factors associated with superficial surgical site infection (SSSI) and investigate their correlation with the progression of periprosthetic joint infection (PJI). The study is clear and well presented. The purpose of the question is relevant, despite several articles published on this topic, still there is room for research in this area to follow on meta-analyses regarding the risk factors for PJI. I have some comments or questions for the authors. 1. In the title appear as a cross-sectional study however, it seems that the nature of the study is retrospective. Please make it clear because the terms are not interchangeable. 2. In the abstract appears that the patients were interviewed ≥3 months after surgery to answer questions about the postoperative period, including any occurrences of SSSI. Please clarify what was the question regarding SSSI. Additionally, in the methods, appear that the patient's records were reviewed to determine whether there had been any documentation of difficulties with wound-healing or whether antibiotics were prescribed to treat an infection related to arthroplasty. Which of these were used as criteria to define the occurrence of SSSI after surgery? How did you integrate the information from records and patients? Please state this clearly in the abstract, methods. 3. Follow-up was a minimum of 5 years (line 92). Please show the mean follow-up time for SSSI and PJI with range and discuss in your document the possibility that the PJI is coming from a different source than the SSSI. This is because you have a very long follow-up. Most infections occur weeks to months after surgery. Late infections are usually spread through the bloodstream from another part of the body. For instance, a urinary tract infection or tooth abscess has been found to cause infections in joint replacements (AAHKS). 4. Please present the mean Age and BMI with SD or range for your cohort. These values have implications in generalizability, perhaps this could explain why your cut point for BMI was 35. If this is not the reason explain why you selected 35 when obesity is considered from 30. 5. Statistics. How did you handle missing values? in table 2 it is possible to notice that you had around 10% with missing data for RA. Perhaps if you use imputed data you could have more power to run your analysis in table 5.

	6. Results. Table 5. You mentioned only male sex as a significant risk factor for progression to PJI in subjects with SSSI. However, the adjusted RR for ASA>=3 is 3,1 (CI=1,0 – 10,0). Do not be misled by the P-value of 0.051 because your analysis there is lacking power. Still, ASA>=3 is important to report as borderline significant in your results and conclusions. In your discussion as well (line 194-495). 7. What about other possible risk factors for SSSI and PJI as excess alcohol, IV drug use, poor oral hygiene, other medical conditions or medications that compromise immunity were considered in the interview or present in records? If so, why were not included?. 8. The discussion seems very short and lacks important information. How are your results compared with other studies on the same topic? What new information are you adding? Check other recent articles on this topic and discuss other factors that you did not include in your study that are important in this association with SSSI and PJI. You mentioned the sample size as a strength however in another part of your document you recognize that the sample size is low for the relation SSSI-PJI. It should be clear, now is contradictory. Please redact better your discussion and make it more reach in analysis.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1 Comments to the Authors:
Hello! I want to first commend you on a job well done. This is a critical concern for TJA and something we hope to always address, research, and minimize for the future.
Author response: Thank you for your comment!

1. There are some newer articles that address the rates of infection in obese patients, especially using NSQIP in the US or other similar databases worldwide. There are quite a few studies in your references that are over 10 (even 20) years old. Given the abundance of research since then, there are more relevant and clinically applicable research articles that should be referenced and included.

Author response: Thank you for pointing this out. We have updated the references accordingly and this has improved the overall discussion with relevant new references, please see page 11, lines 209 -114.

2. There are some speculative studies that look into rates of SSI and PJI by surgeon (attending vs resident, junior vs senior surgeon). Is this a variable you can look into? It would be worthwhile to control for variables such as this.

3. Similarly, the greater the number of people scrubbed into the surgery, I'd speculate that there would be greater rates of infection or bacterial transmission. Can you retroactively review this or at least comment on it in your manuscript?

4. There is a lot of research that shows that the time on the OR table leads to greater rates of morbiditiy and mortality - as there is more time for things to go wrong. Similarly, is this a variable you can look into and control for? I anticipate that there might be a relationship with the rates of SSI and PJI with longer surgeries.

Author response to p. 2-4: Thank you for pointing this out. Although we respectfully agree that this is an important consideration, it is beyond the scope of this manuscript. The focus of this study was to evaluate the patient factors related to SSSI. Even though we are aware that surgery-related factors affect the risk of postoperative infection and we mention that in the discussion part of the manuscript, page 12, line 256-259.
In our unit, elective prosthetic surgery is performed by a consultant orthopedic arthroplasty surgeon to strive for an operation time not exceeding 90 minutes (considering primary elective hip or knee arthroplasty). During surgery maximum of 2 surgeons attends the theatre. We added a comment on that issue in the discussion part of the manuscript, please see page 12 lines 256-259.

5. Regarding age... Now, this specific variable of interest has a lot of sub-components that can reasonably contribute to greater rates of SSI and they are not addressed. As one ages, their nutritional status decreases. Typically, they are not eating as well a rounded diet as before, and their caloric intake may be above or below what is recommended. Other factors that can look at nutritional status include albumin, as this would give a good clinical picture in relation to their diet over the last few months. Also, older patients have decreased collagen and elasticity, as is natural with aging, and therefore have decreased wound healing complexes, which can further be a contributing factor to SSI and PJI. Please consider editing your manuscript to include these in your discussion, and if possible, retroactively comparing nutritional status.

Author response: Thank you for this suggestion. It would have been interesting to explore this aspect further. More specific information regarding the patient's nutritional status was not available. However, all patients undergoing elective surgery at our unit receive information about the importance of a complete and varied nutritional intake. All patients attend a clinical appointment before surgery where the importance of a varied diet is emphasized and nutritional drinks are offered for those who need them. A comment on nutritional status is added in the manuscript, please see page 11 lines 216 – 223.

6. As mentioned, due to the sample size, there is a greater chance for a Type II statistical error but I appreciate you addressing this early in the manuscript.

Lastly, as mentioned, this was a well written and well-researched project. With only a few minor revisions and expansion regarding a few topics of interest, as listed above, it would be ready for publication
Author response: Thank you!

Reviewer: 2.
The authors presented a paper to identify patient-related risk factors associated with superficial surgical site infection (SSSI) and investigate their correlation with the progression of periprosthetic joint infection (PJI). The study is clear and well presented. The purpose of the question is relevant, despite several articles published on this topic, still, there is room for research in this area to follow on meta-analysesegarding the risk factors for PJI.
Author response: Thank you for your comment!
I have some comments or questions for the authors.

1. In the title appear as a cross-sectional study however, it seems that the nature of the study is retrospective. Please make it clear because the terms are not interchangeable.

Author response: Thank you for pointing this out. We have updated the title accordingly.

2. In the abstract appears that the patients were interviewed ≥3 months after surgery to answer questions about the postoperative period, including any occurrences of SSSI. Please clarify what was the question regarding SSSI. Additionally, in the methods, appear that the patient's records were reviewed to determine whether there had been any documentation of difficulties with wound-healing or whether antibiotics were prescribed to treat an infection related to arthroplasty. Which of these were used as criteria to define the occurrence of SSSI after

surgery? How did you integrate the information from records and patients? Please state this clearly in the abstract, methods.

Author response: As suggested, we have clarified this in the abstract. Initially, this information was available in the abstract but was accidentally removed due to the word limit, please see now page 2 lines 32-35.
Questions asked the patients during the interview:

- If the surgical wound had healed and if stitches/clips had been removed according to plan.
- If and how many times the bandage had been replaced postoperatively.
- If the patient had taken antibiotics and if the patient had been cared for in hospital after discharge.

An orthopedic consultant reviewed all information from the patients' records (recorded from general practitioners or orthopedic consultant) including possible wound healing problems or antibiotic prescribing due to suspected postoperative infection. This information and the results of the patient interview were taken under consideration in order to determine the occurrence of SSSI. The diagnosed PJI was determined by a consultant orthopedic surgeon and a consultant in infectious diseases in collaboration. Please see page 4 lines 81-87.

3. Follow-up was a minimum of 5 years (line 92).

Please show the mean follow-up time for SSSI and PJI with range and discuss in your document the possibility that the PJI is coming from a different source than the SSSI.
This is because you have a very long follow-up. Most infections occur weeks to months after surgery. Late infections are usually spread through the bloodstream from another part of the body. For instance, a urinary tract infection or tooth abscess has been found to cause infections in joint replacements (AAHKS).

Author response: We agree with the reviewer's assessment. There is always a risk of hematogenous PJI, not related to the index surgery. We have a meticulous follow up of our patients and we found that none of our patients during our reported follow-up was suffering from hematogenous PJI.

4. Please present the mean Age and BMI with SD or range for your cohort. These values have implications in generalizability, perhaps this could explain why your cut point for BMI was 35. If this is not the reason explain why you selected 35 when obesity is considered from 30.

Author response: Thank you for this suggestion, we have added the suggested content to the manuscript on SD for age and BMI, please see table 2.
Further, we agree with the reviewer's assessment regarding BMI. Accordingly, throughout the manuscript, we have divided the thresholds for BMI according to the WHO definition but instead of using all 5 groups we divided them into 3; BMI<25 (under- and normal weight), 25≤BMI<30 (overweight), BMI≥30 (obesity). Patient with underweight and normal weight was put in the same group and patients with obesity in the same group, due to few patients in each group. We have made all the analyses with this updated data, please see table 3, 4; page 8, lines 158-162; page 9, line 175-177.

5. Statistics. How did you handle missing values? in table 2 it is possible to notice that you had around 10 % with missing data for RA. Perhaps if you use imputed data you could have more power to run your analysis in table 5.

Author response: We think this is an excellent suggestion but instead of imputing data (not possible on RA variable), we excluded those patients where information regarding RA was

missing and we made the analysis with the new patient cohort. Please see please see table 3, 4 (table 5 earlier); page 8, lines 158-162; page 9, line 175-177.

6. Results. Table 5. You mentioned only male sex as a significant risk factor for progression to PJI in subjects with SSSI. However, the adjusted RR for ASA>=3 is 3,1 (CI=1,0 – 10,0). Do not be misled by the P-value of 0.051 because your analysis there is lacking power. Still, ASA>=3 is important to report as borderline significant in your results and conclusions. In your discussion as well (line 194-495).

Author response: We totally agree that the p-value can be misleading. In line with your suggestion we have divided the thresholds for BMI according to the WHO definition, as mentioned above (comment nr 4) and re-run the analyses. ASA classification is now a statistically significant factor but male sex failing but close to being statistically significant. That result is of course due to lack of power in our cohort with the risk for type II error. We comment that in the limitation section of the discussion and we specially discuss RA and male sex as risk factors (but not statistically significant). We have updated the results, please see page 8, lines 158-162. Further, we have commented on this in the discussion, please see page 11, lines 229-231.

7. What about other possible risk factors for SSSI and PJI as excess alcohol, IV drug use, poor oral hygiene, other medical conditions or medications that compromise immunity were considered in the interview or present in records? If so, why were not included?

Author response: Thank you for pointing this out. According to preoperative screening routines in our hospital patients with a history of excessive use of alcohol, IV drug use, poor oral hygiene or other medical conditions or medications that compromise immunity referred to our unit for primary arthroplasty are excluded from surgery or already rehabilitated before surgery. The discussion has been updated regarding how patients with conditions that may compromise the ability to heal after arthroplasty surgery are handled in our unit, please see page 13, lines 273 – 277.

8. The discussion seems very short and lacks important information. How are your results compared with other studies on the same topic? What new information are you adding? Check other recent articles on this topic and discuss other factors that you did not include in your study that are important in this association with SSSI and PJI. You mentioned the sample size as a strength however in another part of your document you recognize that the sample size is low for the relation SSSI-PJI. It should be clear, that now is contradictory. Please redact better your discussion and make it more reach in analysis.

Author response: Thank you for the comment. We revised out manuscript thoroughly. Accordingly, we have redacted the discussion part of the manuscript adding all useful information and comments suggested by all reviewers and updated the overall structure of the discussion, please see pages 10-14.

The patient risk factors for developing PJI after TJA is well described earlier. However the patient risk factors and the occurrence of SSSI after TJA are not well described in the literature. We tried to address these unanswered questions with our study. We exclusively included patients with primary elective joint surgery in order to minimise the influence of other risk factors concatenated with the initial trauma (hip fractures) or extended impact on the tissue (revision surgery) which are used in other studies. We also have a meticulous follow up of the patients without missing any important information that could affect our results. We are aware that other factors especially related to the surgery (operation time, intraoperative blood loss, discipline in the operating room, antibiotic-prophylaxis used, surgeon's experience etc) can affect the overall risk for postoperative infection, but those are not included in this current analysis. The focus/span> of our study was preoperatively and we tried to identify the patient-related risk factors for SSSI and subsequently PJI. Additionally, primary TJA in our hospital is a strictly defined standard procedure and the differentiation on the surgery-related factors should be minimal but we recognise that potentially affect our results.

We understand that the statement “the big sample size is a strength of our study” and at the same time we mention the risk of type II error due to lack of power, can be contradictory. However, it is well known that infection-related research, in general, is a major challenge due to the low infection rate after TJA. Our study is one of the largest studies addressing the issue of SSSI after TJA but still may fail to come up with statistically significant results due to the low infections rates. We comment on that in our manuscript.
Identification and optimization of risk factors for progression of SSSI may decrease the risk of subsequent PJI. Randomized studies would be desirable but it is difficult to perform, not least because of the low incidence of infections. We think (and we hope that you share our opinion) that the results of our study are relevant and offer new insight concerning the relationships between patient-related risk factors for SSSI and their correlation to the risk of PJI development.

VERSION 2 – REVIEW

REVIEWER	Castano-Betancourt, Martha Cecilia FMJ, Postgraduate
REVIEW RETURNED	24-May-2022

GENERAL COMMENTS	Dear authors, Thanks for addressing my questions. I appreciate the fact that you corrected the analyses according to the raised points (BMI categories, ASA>3 significance) confirming the results and making stronger the manuscript. The only point that I consider was not presented is the mean follow-up time for SSSI, perhaps you could not estimate the exact point through the records and the patients are not able to determine it. I still consider you should briefly mention this. In some parts of the manuscript, the grammar and punctuation can be improved by still the manuscript it is easy to understand.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2.

Dear authors,
Thanks for addressing my questions. I appreciate the fact that you corrected the analyses according to the raised points (BMI categories, ASA>3 significance) confirming the results and making stronger the manuscript. The only point that I consider was not presented is the mean follow-up time for SSSI, perhaps you could not estimate the exact point through the records and the patients are not able to determine it. I still consider you should briefly mention this. In some parts of the manuscript, the grammar and punctuation can be improved by still the manuscript it is easy to understand.

Author response: Thank you for this suggestion, we have updated the manuscript to make this more clear, please see page 2, line 31 and page 4, line 79.

We found all cases of SSSI within the interview period (3-5 month after index surgery) and patient medical records for all patients were reviewed for the total follow-up period of 5 years (mean 7.3; range 5.1-9.2) regarding the occurence of SSSI or PJI.

Further, we have used an editing service for a thorough proofread of the text.