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Patient-dependent risk factors for wound infection after skin surgery: A systematic review and meta-analysis

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Abstract

Postoperative wound infection in dermatologic surgery causes impaired wound healing, poor cosmetic outcome and increased morbidity. Patients with a high-risk profile may benefit from perioperative antibiotic prophylaxis. The objective of this systematic review was to identify risk factors for surgical site infection after dermatologic surgery. In this article, we report findings on patient-dependent risk factors. The literature search included MEDLINE, EMBASE, CENTRAL and trial registers. We performed meta-analysis, if studies reported sufficient data to calculate risk ratios with 95% confidence intervals. Study quality was assessed according to the Newcastle-Ottawa-Scale. Seventeen observational studies that analysed 31213 surgical wounds were eligible for inclusion. Fourteen studies qualified for meta-analysis. Nine studies showed good, three fair and five poor methodological quality. The reported incidence of surgical site infection ranged from 0.96% to 8.70%. Meta-analysis yielded that male gender and immunosuppression were significantly associated with higher infection rates. There was a tendency towards a higher infection risk for patients with diabetes, without statistical significance. Meta-analysis did not show different infection rates after excision of squamous cell carcinoma or basal cell carcinoma, but studies were substantially heterogenous. There was no significant association between risk for wound infection and smoking, age over 60 years, oral anti-aggregation or anti-coagulation or excision of malignant melanoma. In conclusion, the risk for surgical site infection in dermatologic surgery is low. Infection rates were increased significantly in male as well as immunosuppressed patients and non-significantly in diabetics.

KEYWORDS

dermatological surgery, perioperative antibiotic prophylaxis, postoperative wound infection, skin surgery, surgical site infection

Abbreviations: BCC, basal cell carcinoma; CI, confidence interval; NOS, Newcastle-Ottawa Scale; OR, odds ratio; PAP, perioperative antibiotic prophylaxis; RR, relative risk; SCC, squamous cell carcinoma; SSI, surgical site infection.

Key Messages

- dermatologic surgeons frequently and inconsistently use perioperative antibiotic prophylaxis, despite low rates of wound infection
- we performed a systematic review and meta-analysis in order to summarise the current evidence on risk factors for surgical site infection in skin surgery
- this article focusses on patient-related risk factors
- infection rates are higher in men and immunosuppressed patients and non-significantly increased in individuals with diabetes

1 | INTRODUCTION

Surgical site infection (SSI) causes impaired wound healing and increased morbidity. Given the low incidence of SSI in dermatologic surgery, there is an ongoing debate, whether perioperative antibiotic prophylaxis (PAP) is appropriate.[1] In addition, it remains unclear if PAP may sufficiently prevent SSI.[2,3] According to a consensus statement, PAP may be considered in certain high-risk procedures involving specific body sites, such as the nose, lips or ears, among others.[4] Thus, patients with multiple risk factors for SSI may benefit from antibiotic prophylaxis. To assess the efficacy of PAP in clinical studies, relevant risk factors need to be identified. Therefore, we performed a systematic review and meta-analysis to critically summarise the current evidence. In this article, we report our results on patient-related risk factors.

2 | METHODS

We conducted a systematic literature search in May 2021, which included MEDLINE, Embase, Cochrane Central Register of Controlled Trials (CENTRAL) and the following trial registers: controlled-trials.com, ClinicalTrials.gov, http://www.anzctr.org.au, www.who.int/trialsearch/, and clinicaltrialsregister.eu. The search string is provided as supplement (Appendix S1). The search for relevant records also included the reference lists of included studies. Prior to this review, a protocol was published in PROSPERO, the international prospective register of systematic reviews (CRD42020180435). Differences between review and protocol are provided as supplement (Appendix S2).

Observational studies, controlled clinical trials and case–control trials were feasible for inclusion. A table which summarises the reasons for exclusion of identified studies is provided as a supplement (Appendix S3).

Two authors (J.G.S., K.P.) screened titles and abstracts that were identified by database searches. Both authors also independently analysed full texts of all potentially relevant titles and abstracts. Only one author (J.G.S.) searched in trial registers for potentially feasible ongoing records. Relevant study data were independently extracted by three authors (J.G.S., K.P., V.R.) by using an internally piloted data extraction sheet (Microsoft Excel 2010). The risk of bias of all included studies was assessed by the same three authors using the Newcastle-Ottawa-Scale (NOS).[5] We graded the study quality as 'good', 'fair' or 'poor' based on thresholds as proposed by McPheeters et al.[6]

Studies qualified for meta-analysis, if authors provided sufficient data to calculate risk ratios (RR) for the following factors: age over 60 years, gender, diabetes, immunosuppression, smoking, excision of malignant melanoma, basal cell carcinoma (BCC) or squamous cell carcinoma (SCC), as well as anti-coagulation or anti-platelet medication. We used the random-effects models with the Mantel-Hanszel method for data synthesis, as we expected clinical and methodological heterogeneity between studies. The I^2-index served to quantify heterogeneity. As recommended by the Cochrane Collaboration, we interpreted values of I^2 between 0% and 40% as not important, 40% and 60% as moderate, 60% and 90% as substantial and 90% and 100% as considerably heterogeneous.[7] We intended to explain substantial heterogeneity among the studies by differences in design, cohort or surgical setting. We presented study results narratively, if studies did not provide feasible statistical information to be included for meta-analysis. Statistical analysis was performed in R statistics, version 4.0.3, R Foundation for Statistical Computing.

3 | RESULTS

We identified 17 feasible observational studies that analysed 31213 surgical wounds (Figure 1).[8-24] Fourteen studies qualified for meta-analysis. The reasons for exclusion of other identified studies are summarised in Appendix S3.

Table 1 summarises the characteristics of the included studies. Most studies were conducted in dermatology departments, while two studies were performed in

surgery and general medicine, respectively. The incidence of SSI ranged from 0.96% to 8.70%. The smallest study included 134 and the largest 5091 surgical procedures. Seven studies focussed on interventions in the ambulatory and six on the inpatient setting. Four studies included both in- and outpatients for analysis.

Based on the NOS, nine studies showed good, three fair and five poor quality (Table 1). Participants were truly or somewhat representative in most studies. Study authors only assessed patients from the same respective study site and extracted relevant data from hospital or study records. Nine studies did not clearly state whether the surgical site showed signs of infection prior to the intervention. Five studies had a very short follow-up period after surgery. This might have resulted in a lower detection rate of wound infections. There was no relevant loss to follow-up in any study in order to introduce bias.

According to the meta-analysis including nine studies, male patients had a significantly higher risk for wound infection after skin surgery (RR 1.51, confidence interval [CI] 1.24-1.85, $I^2 = 0\%$, Figure 2).[8,13-19,23] These data are based on six prospective and three retrospective studies. Five studies had good and two fair or poor quality, respectively. Two additional studies did not report sufficient data to be included for meta-analysis: A large prospective study of good quality with 3491 patients confirmed the significantly higher risk for SSI in male patients (OR 5.46, CI 1.12-26.54, $P = .035$).[9] In contrast, a retrospective study of poor quality including 512 individuals did not detect a significant difference in SSI

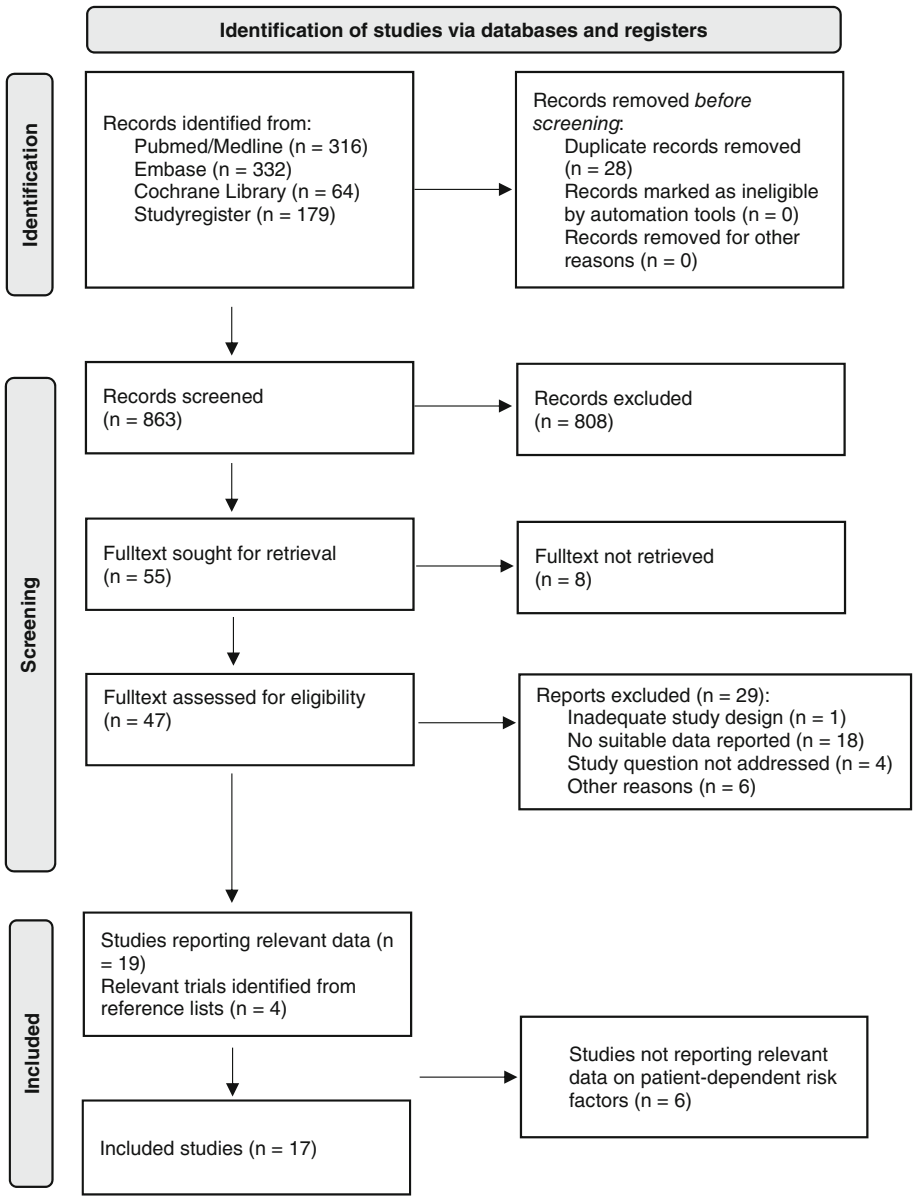

FIGURE 1 PRISMA-Studyflow diagram, adapted and modified from Reference 28

TABLE 1 Characteristics of the included studies

No.	Study	Medical discipline	Study design	Incidence of SSI (%)	N = patients/ interventions	Age	PAP included	Setting of surgery	Type of surgical procedures	Additional information	Study quality
1	Liu et al (2018)	Dermatology	PSOS	4.00	1977 interventions	66.2	No	Out- and inpatients	Dermatosurgical procedures in local anaesthesia	Minor interventions (e.g. biopsies) excluded	Good
2	Heal et al (2006)	General Medicine	PMOS	8.60	857 patients	56.3	No	Ambulatory care	Minor excisions (one-layer)	Surgery performed by GP	Good
3	Heal et al (2012)	General Medicine	PMOS	8.70	972 patients	59.3	No	Ambulatory care	Minor excisions (two-layer) including skin flaps	Surgery performed by GP	Good
4	Bordeaux et al (2011)	Dermatology	PSOS	1.30	1911 patients	Not reported	Yes	Outpatients	Dermatosurgical procedures	Minor interventions (e.g. biopsies) excluded	Fair
5	Rogues et al (2007)	Dermatology	PMOS	1.90	3491 patients	51.4	Yes	Out- and Inpatients	Dermatosurgical procedures	Infected sebaceous cysts and pyoderma excluded.	Good
6	Kulichová et al (2013)	Dermatology	PSOS	1.90	3284 interventions	Not reported	Yes	Inpatients	Dermatosurgical procedures		Poor
7	Amici et al (2005)	Dermatology	PMOS	2.00	3788 patients	51.5	Yes	Out- and inpatients	Dermatosurgical procedures	Infected sebaceous cysts and pyoderma excluded.	Poor
8	Dixon et al (2006)	Dermatology	PSOS	1.47	5091 interventions	57.5	Not reported	Inpatients	Dermatosurgical procedures	Skin graft donor sites were not included for analysis.	Good
9	Rhinehart et al (2006)	Dermatology	RSCS	1.80	1400 interventions	66.8	No	Ambulatory care	MMS	Delayed wound closure excluded.	Good
10	Balakirski et al (2020)	Dermatology	RMCS	6.70	134 interventions	74	Yes, but not as SSI-prophylaxis	Inpatients	MMS	Only immunosuppressed patients analysed	Fair
11	Balakirski et al (2018)	Dermatology	RSCS	6.70	284 interventions	77	No	Inpatients	Dermatosurgery	Minor interventions (e.g. simple excisions) excluded.	Fair

(Continues)

TABLE 1 (Continued)

No.	Study	Medical discipline	Study design	Incidence of SSI (%)	N = patients/ interventions	Age	PAP included	Setting of surgery	Type of surgical procedures	Additional information	Study quality
12	Penington et al (2010)	Surgery	PSOS	7.25	924 interventions	64.5	Not reported	Outpatients	Procedures in local anaesthesia	Biopsies excluded.	Poor
13	Nakamura et al (2021)	Dermatology	RSCS	5.50	512 patients	60	Yes	Outpatients	Procedures in local anaesthesia	Surgery of subcutaneous tumours (e.g. lipoma) excluded	Poor
14	Schmitt et al (2018)	Dermatology	RSCS	5.00	331 interventions	74	Yes	Outpatients	Only complex repairs analysed		Good
15	Toia et al (2012)	Plastic surgery	PSOS	0.96	517 interventions	58.1[a]	No	Inpatients	Skin surgery and mucosal excisions	Only data of "group 1" which underwent skin surgery considered for this review	Good
16	Dettenkofer et al (2003)	Dermatology	PSOS	2.1	995 interventions	Not reported	Not reported	Inpatients	Dermatosurgery	Study focused on nosocomial infections in general. No follow-up after discharge performed.	Poor
17	Basu et al (2019)	Dermatology	RSCS	1.8	4745 interventions	69.3[b]	Not reported	Outpatients	MMS	This study compared postoperative complications rates between immunosuppressed and -competent patients	Good

Abbreviations: GP, general practitioner; MMS, Moh's micrographic surgery; PAP, perioperative antibiotic prophylaxis; PMOS, prospective multi-centre observational study; PSOS, prospective single-center observational study; RMCS, retrospective multi-center cohort study; RSCS, retrospective single-center cohort study.

[a]This was the mean age of the study cohort, which also included patients that received interventions beyond the scope of dermatologic surgery.

[b]Computed, mean age reported for patients with and without surgical complications separately.

incidence between both sex (OR 1.71, CI 0.78-3.72, $P = .179$).[10]

Meta-analysis of three studies showed no difference in the risk for SSI between individuals older or younger than 60 years (RR 2.07, CI 0.55-7.80, $I^2 = 14\%$, Figure 3).[13,15,23] Heterogeneity was not important. All three studies included in this analysis were performed prospectively with good quality. Three additional studies analysed the SSI risk depending on patients' age, but the reported age groups could not be separated into patients older or younger than 60 years. Inclusion for meta-analysis was therefore not feasible. A large prospective study of good quality analysed 1977 interventions and performed multivariate logistic regression. There was no significant difference in wound infection rate between patients older and younger than 65 years (OR 0.99, CI 0.97-1.01, $P = .40$).[14] According to a prospective study including 3788 patients, individuals older or younger than 50 years did not have a significantly different risk for wound infection (OR 1.2, CI 0.7-1.9).[8] However, another large prospective study analysing 3784 interventions reported a higher SSI risk for patients over 70 years. All severe wound infections and 68% of mild SSI occurred in this age group.[19] The latter two studies showed poor methodological quality.

Meta-analysis including eight studies showed a tendency towards a higher risk for SSI for patients with diabetes without statistical significance (RR 1.48, CI 0.98-2.23, $I^2 = 0\%$, Figure 4).[8,10,12-15,18,23] Heterogeneity was not important. This finding is based on six prospective and two retrospective studies. Five studies showed good, one fair and two poor quality. One additional study analysed diabetes as potential risk factor for SSI but could not be included for meta-analysis due to the lack of feasible data.[22] The authors assessed 924 interventions and found no different SSI rate in patients with diabetes (OR 3.0, CI 0.7-9.3). However, only 22 patients had diabetes and study quality was poor.

Meta-analysis of five studies yielded a significantly higher risk for wound infection in immunocompromised patients (RR 2.11, CI 1.02-4.39, $I^2 = 54\%$, Figure 5).[8,10,14,17,20] Heterogeneity was moderate. Six studies were prospective and two retrospective. Two studies showed good, one fair and two poor study quality. Results from a prospective study of good quality with 3491 patients confirmed the significantly higher SSI risk

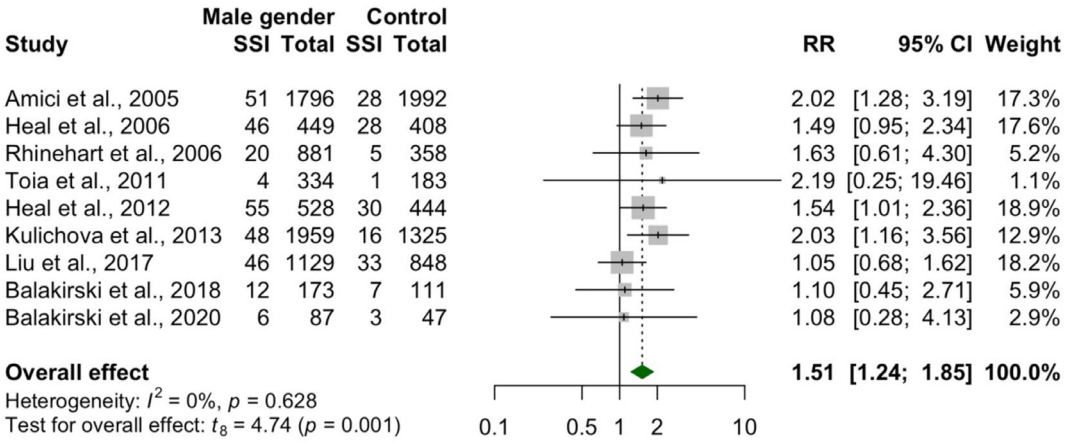

FIGURE 2 Meta-analysis: male gender

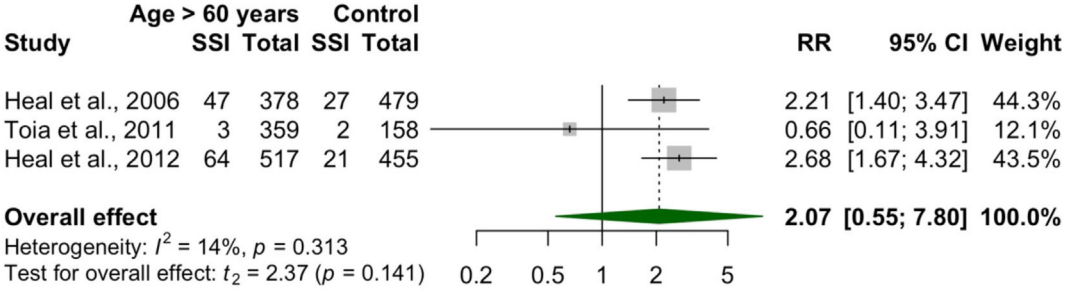

FIGURE 3 Meta-analysis: age over 60 years

for immunosuppressed individuals (OR 9.99, CI 1.83-54.3).[9] However, this study did not report data that could feasibly be included for meta-analysis.

Meta-analysis including four studies showed that smoking did not affect the risk for wound infection (RR 0.80, CI 0.47-1.36, $I^2 = 0\%$, Figure 6).[8,12,13,23] Heterogeneity was not important. All studies were performed prospectively, three with good and two with poor quality.

Meta-analysis of five studies showed no risk difference for SSI after excision of malignant melanoma (RR 0.91, CI 0.09-8.89, $I^2 = 50\%$, Figure 7).[10,13,16,17,21] Heterogeneity was moderate. This finding is based on two prospective and three retrospective studies. Two were graded as good, one as fair and the remaining two studies as poor quality.

Meta-analysis of six studies found no risk difference for wound infection after excision of BCC (RR 1.15, CI 0.47-2.80, $I^2 = 73\%$, Appendix S4—Figure 1).[10,13,15-17,21] Three studies were prospective and retrospective, respectively. Quality was good in three, fair in one and poor in two studies. However, heterogeneity was substantial, and the direction of effect varied. This may be explained by clinical and methodological heterogeneity. The authors Dettenkofer et al performed a prospective surveillance study in order to detect all kind of nosocomial infections.[21] Investigators were not included in patient care, assessed only patients hospitalised for more than 48 hours and did not perform follow-up visits after discharge. Therefore, SSI may not have been sufficiently detected, which may have introduced bias. In contrast, the authors Nakamura et al and Rhinehard et al performed retrospective studies in the outpatient setting. Both found a tendency towards a lower risk of SSI after BCC excision.[10,16] However, given the substantial heterogeneity and variation in the direction of effect, the pooled effect estimate is highly uncertain.

Meta-analysis of six studies showed a tendency towards a higher risk for wound infection after excision of SCC (RR 2.24, CI 0.92-5.42, $I^2 = 70\%$, Appendix S4—Figure 2).[10,13,15-18] Two studies were prospective and four retrospective. Three studies showed good, two fair and one poor quality. Heterogeneity among the studies was substantial. The direction of effect varied in one retrospective study that compared SSI rates between hospitalised immunocompromised and immunocompetent patients. One retrospective multicentre study only assessed immunocompromised individuals that underwent extensive dermatosurgical procedures as inpatients.

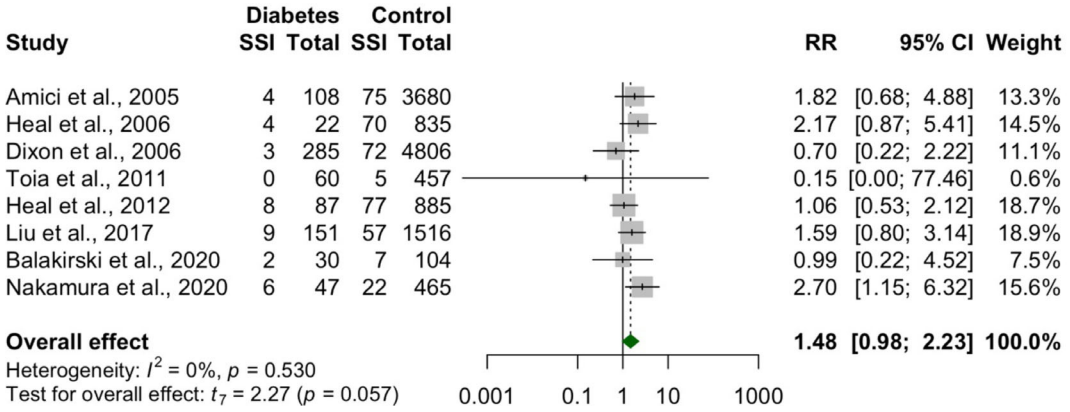

FIGURE 4 Meta-analysis: diabetes

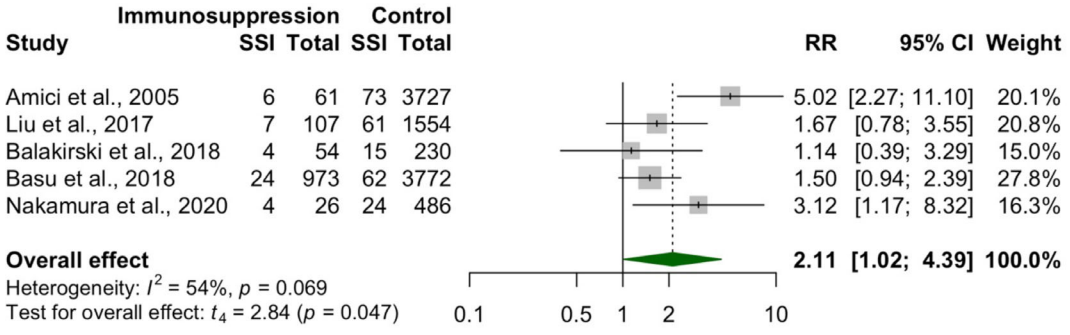

FIGURE 5 Meta-analysis: immunosuppression

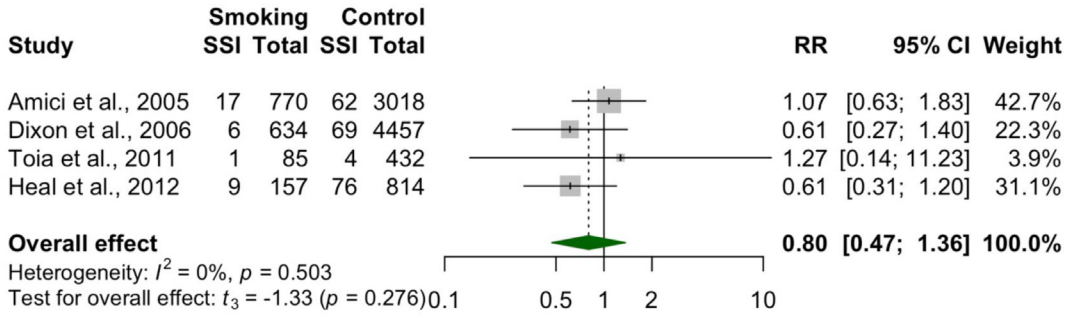

FIGURE 6 Meta-analysis: smoking

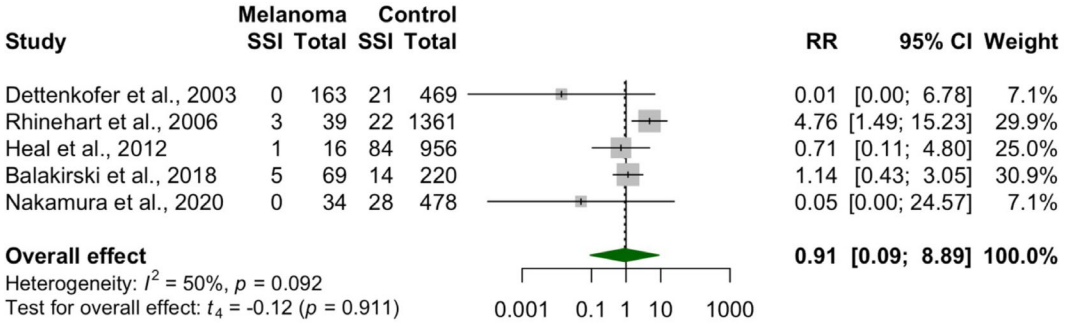

FIGURE 7 Meta-analysis: excision of malignant melanoma

Two prospective studies included patients that underwent small procedures performed by a general practitioner.[13,15] However, this may not sufficiently explain differences in the direction of effect, which is therefore linked to uncertainty.

Meta-analysis of four studies did not show a significant association between SSI and anti-platelet medication, such as aspirin or Clopidogrel (RR 1.35, CI 0.65-2.78, $I^2 = 37\%$, Appendix S4—Figure 3).[8,12,13,24] These results are based on two prospective and one retrospective study of good quality and one prospective study of poor quality. Heterogeneity was not important. In addition, two prospective studies including 1911 and 927 interventions, respectively, could not be included due to insufficient data reporting. However, results of both studies are in line with meta-analysis that anti-platelet therapy did not affect the SSI rate (aspirin: OR 0.83, CI 0.35-1.7[22] and OR 0.90, CI 0.39-2.09[11]; Clopidogrel: OR 1.23, CI 0.16-9.21[11]). One study had fair, the other, poor quality.

Meta-analysis of five studies showed no significantly different SSI rate in patients taking oral anti-coagulants (RR 1.66, CI 0.79-3.49, $I^2 = 0\%$, Appendix S4—Figure 4).[8,10,12,13,24] Heterogeneity was not important. Three studies were prospective and two were retrospective. Methodological quality was good in three and poor in two studies. One prospective study including 1911 participants did not qualify for meta-analysis since authors did not report feasible data. However, according to this study of fair quality, patients on Coumadin did not show a different SSI risk (OR 2.49, CI 0.84-7.36).[11]

Meta-analysis of three studies yielded, that patients on both anti-platelet and anti-coagulant medication did not have a different risk for wound infection (RR 4.55, CI 0.09-2.27, $I^2 = 0\%$, Appendix S4—Figure 5).[12,18,24] In all studies, the number of participants under anti-platelet and anti-coagulant treatment was low, which is reflected by the wide confidence interval. Heterogeneity among both retrospective and one prospective study was not important. Two showed good and one fair study quality.

4 | DISCUSSION

This article summarises the current evidence on patient-dependent risk factors for SSI in dermatologic surgery. The overall incidence of SSI in skin surgery was low. Male gender and immunosuppression were associated with significantly higher infection rates. There was good evidence that diabetes may be linked to a higher infection risk as well. The risk of SSI after SCC or BCC excision remains uncertain. Other factors, such as smoking, age over 60 years, oral anti-coagulation or anti-aggregation,

and excision of malignant melanoma did not show any substantial association with wound infection.

Diabetes compromises the immune response and is widely considered as potential risk factor for wound infection after surgery.[25] Although meta-analysis did not reach statistical significance, heterogeneity among studies was not important, and most data are based on trials of good quality. Therefore, it is possible that diabetes may be considered as an independent risk factor for SSI in dermatologic surgery as well. Excision of SCC showed a statistical tendency towards a higher risk for wound infection as well. However, studies were methodologically and clinically heterogenous. In addition, the direction of effect varied, and most data are based on retrospective studies. The potential infection risk may be explained by the presence of ulceration. However, the latter is also common in BCC, which did not show any statistical association with postoperative wound infection. Studies analysing the risk for wound infection after BCC excision were substantially heterogeneous as well. Hence, it remains uncertain, whether excision of SCC or BCC may affect the SSI rate.

Smoking has a significant impact on wound healing.[26] However, meta-analysis of well-conducted large prospective studies showed no association between smoking and wound infection after skin surgery. Interestingly, there was good evidence that men have a higher risk for wound infection. This may be explained in different health behaviour and compliance of male patients. Given the moderate heterogeneity among studies and confirmatory data of a large prospective study of good quality, there is good evidence that immunocompromised patients inherit a higher SSI risk. We included all types of immunosuppression for data synthesis. If specific individual immunosuppressive treatments or conditions lead to a different wound infection risk, further research is needed. Elderly patients may develop various risk factors for SSI. However, data synthesis did not show higher infection rates in patients of higher age. This may be due to our predefined cut-off of 60 years, which could have been too low to detect a significant difference. As prescribed by the authors Kulichova et al the geriatric population may have higher infection rates, but there is not enough data to support this assumption.[19]

There are few systematic reviews that assess risk factors for SSI in dermatologic surgery and none that performed meta-analysis, to our knowledge. Our findings are mostly in line with those of a systematic review, which focussed on minor skin interventions, even though we additionally included studies on complex dermatologic surgery.[27] In contrast, however, our data do not provide supportive evidence that excision of SCC or BCC are associated with SSI.

This systematic review has certain limitations. Not all identified potentially relevant studies could be included since we could not obtain all full texts. In addition, the SSI risk after excision of SCC and BCC remains uncertain due to substantial heterogeneity among studies. However, given the wide spectrum of skin surgery, we expected heterogeneity among the included studies and thus interpreted the data in the light of methodological or clinical differences between the studies. Although this article focusses on a small number of factors, the true risk for SSI probably depends on a combination of various risk factors, including the type of surgery and the operated body site, which could not be taken into account in this article.

The incidence of wound infection in dermatologic surgery is low. It will therefore be challenging to statistically detect whether prophylactic antibiotics prevent SSI. Our findings help to identify patients at risk for wound infection that may benefit from PAP. However, whether systemic antibiotics can effectively prevent SSI in dermatologic surgery needs to be assessed in large controlled clinical trials.

5 | CONCLUSION

Overall, the incidence of SSI in skin surgery is low. Men, immunocompromised individuals and probably patients with diabetes have a higher risk for wound infection. The infection risk after excision of SCC or BCC remains uncertain. Smoking, age older than 60 years, blood thinners or excision of malignant melanoma may not affect the infection rate.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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