Meta-Analysis of Methicillin-Resistant *Staphylococcus aureus* Colonization and Risk of Infection in Dialysis Patients

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ABSTRACT

Patients undergoing dialysis are particularly vulnerable to methicillin-resistant *Staphylococcus aureus* (MRSA) infections. We performed a meta-analysis of published studies to estimate the prevalence of MRSA colonization in dialysis patients, time trends, and long-term risk of subsequent MRSA infections. Our search of the PubMed and Embase databases returned 5743 nonduplicate citations, from which we identified 38 relevant studies that included data on 5596 dialysis patients. The estimated prevalence of MRSA colonization was 6.2% (95% confidence interval [95% CI], 4.2% to 8.5%). The prevalence increased over time but remained stable after 2000. Stratification of patients according to dialysis modality and setting revealed that 7.2% (95% CI, 4.9% to 9.9%) of patients on hemodialysis were colonized with MRSA compared with 1.3% (95% CI, 0.5% to 2.4%) of patients on peritoneal dialysis (P=0.01), and that a statistically significant difference existed in the percentage of colonized inpatients and outpatients (14.2% [95% CI, 8.0% to 21.8%] versus 5.4% [95% CI, 3.5% to 7.7%], respectively; P=0.04). Notably, the risk of developing MRSA infections increased among colonized hemodialysis patients compared with noncolonized patients (relative risk, 11.5 [95% CI, 4.7 to 28.0]). The long-term (6–20 months) probability of developing a MRSA infection was 19% among colonized hemodialysis patients compared with only 2% among noncolonized patients. In summary, 6.2% of dialysis patients are MRSA colonized, and the average prevalence of colonization has remained stable since 2000. Colonization in hemodialysis patients is associated with increased risk of MRSA infection.

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Invasive methicillin-resistant *Staphylococcus aureus* (MRSA) infections are associated with mortality that is as high as 30%.[1] ESRD patients have a 100-fold higher risk of MRSA infection compared with the general population.[2] Among 80,461 invasive MRSA infections in 2011, 15,169 (18.9%) were among dialysis patients.[3] Although a significant proportion of *S. aureus* infections are of endogenous origin,[4] the relative risk of MRSA infections in colonized patients in this population is largely unknown. Our aim is to comprehensively assess the available data and give a global picture of MRSA colonization among dialysis patients. In this systematic review and meta-analysis, we estimate the prevalence of MRSA colonization among ESRD patients on dialysis treatment and study the significance of MRSA colonization in this population.

RESULTS

The electronic database search yielded 2725 articles from PubMed (from 1922 to October 2013) and 5135 from Embase (from 1958 to October 2013). After removing 2117 duplicate citations, 5743 remained for evaluation. Our database search was

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last updated to include citations published in PubMed and Embase up to October 19, 2013. After scrutinizing the titles and abstracts of retrieved articles, we identified 132 potentially relevant studies, which were reviewed in full text. Of these, 42 studies met our inclusion criteria and were subjected to the meta-analysis. Thirty-five studies were excluded because they did not refer to a screening process performed for detection of MRSA colonization among dialysis patients. In addition, 45 studies did not specify the number of MRSA colonized patients among those who were positive for *S. aureus*, and 3 studies reported data on a specific subpopulation of available dialysis patients (*e.g.,* aged≥65) and were also excluded, as were 3 articles that measured the percentage of MRSA isolates among strains and not among patients. We also excluded two articles in which the screening was performed before the first dialysis session[5,6] and one study in which the patients were treated with nasal decolonization.[7] Finally, one study did not include nasal swabs in its protocol and was excluded.[8] Two additional studies were identified through hand-searching of the reference list of eligible studies (Figure 1).

Of the 44 eligible studies identified, 6 contained overlapping data.[9–14] For these studies, only a single set of data was used in the meta-analysis, leaving 38 suitable studies for data analysis (coded from 44 articles). The 38 studies meeting inclusion criteria provided screening data on 5596 dialysis patients. Of note is that the vast majority (4463 patients) was from studies published within the last decade. The characteristics of the eligible studies are summarized in Table 1.[15–52]

Most of the studies were prospective or cross-sectional (37 of 38; 97%) and only one study was retrospective. On the basis of the Newcastle-Ottawa scale, all studies were deemed of high quality. Fifteen studies were conducted in Europe, 12 in North America, 9 in Asia, and 2 in Africa. No studies from South America and Oceania were identified. The most common country of origin was the United States with 10 studies, followed by Taiwan with 4. The summary prevalence estimates are presented in Table 2. Among the included studies, the estimated prevalence of MRSA colonization in dialysis patients was 6.2% (95% confidence interval [95% CI], 4.2% to 8.5%) (Figure 2) and there was no evidence of publication bias (Egger's bias, −0.78; P=0.58).

Across the 34 studies in the outpatient setting, 13 performed multiple screenings per patient to identify MRSA colonization. Notably, the prevalence of MRSA colonization among these studies was not significantly different from the 16 studies that performed a single screening per patient (P=0.07). Across the remaining five studies, the authors also performed multiple screenings per patient, but required two positive culture results to define the carrier state. Again, this policy did not significantly affect the rate of MRSA colonization compared with studies in which only one screening was performed (P=0.10) (Table 2). All inpatients were screened once (five studies). Moreover, all studies used culture methods for isolation of MRSA and 26 of 38 studies performed the screening only by nasal swabs, whereas in the remaining 12 studies the authors also evaluated extranasal sites (*e.g.*, axilla, groin, perineum, rectum, vascular access site, and catheter exit site). The prevalence of MRSA among patients who had only their nares swabbed was 7.1% (95% CI, 4.6% to 10.0%), and it was not different from studies that also included sampling of extranasal sites (P=0.28).

The pooled MRSA prevalence from European studies was 4.0% (95% CI, 1.5% to 7.7%) and it was lower than the prevalence among the United States studies (7.9%; 95% CI, 4.4% to 12.3%), whereas the corresponding figure among Asian studies was 10.3% (95% CI, 5.7% to 16.0%). Across 5 of 38 studies that focused on hospitalized patients, the estimated prevalence of MRSA colonization upon admission was 14.2% (95% CI, 8.0% to 21.8%), which was significantly higher compared with nonhospitalized chronic renal patients (5.4%; 95% CI, 3.5% to 7.7%; P=0.04).

The index year of all eligible articles was used to study the time trends of MRSA colonization among dialysis patients. An increasing trend was observed over the years among all studies (Figure 3A). Of note is that nine studies did not report the time frame of the screening process and could not be included in modeling the course of MRSA prevalence over time.[27–29,37–41,50] For the sensitivity analysis, we excluded the studies that were conducted before 2000 and we found that the trend of MRSA colonization has stabilized thereafter (Figure 3B).

Twenty-nine of 38 studies included data exclusively from hemodialysis patients, whereas 5 of 38 studies reported data exclusively on peritoneal dialysis patients and 2 of 38 studies included stratified data on both hemodialysis and peritoneal dialysis patients.[28,48] The two remaining studies reported nonstratified data and were not included in this subanalysis.[33,41] Interestingly, the estimated MRSA colonization was 7.2% (95% CI, 4.9% to 9.9%) among hemodialysis patients and 1.3% (95% CI, 0.5% to 2.4%) among peritoneal dialysis patients (P=0.01).

A total of 6 of 38 studies included in our meta-analysis reported data on the MRSA infection rate among MRSA colonized and noncolonized hemodialysis patients.[28,30,33,42,43,46] Two of these studies reported the MRSA infection rate during hospitalization of inpatient individuals,[33,43] whereas four studies included data after a long-term follow-up period of outpatient individuals.[28,30,42,46] Because we were interested in the long-term risk of acquiring a MRSA infection, only the data from the latter four studies were used and the data from each study are summarized in Table 3. The estimated risk of MRSA infection was 3.1% (95% CI, 1.9% to 4.7%). The duration of follow-up among these studies was between 6 and 20 months. The relative risk for MRSA colonized hemodialysis patients to develop a MRSA infection (compared with noncolonized patients) was estimated at 11.5 (95% CI, 4.7 to 28.0; τ^2=0). The combined sensitivity of screening for MRSA infections was 0.55 (95% CI, 0.32 to 0.77), whereas the combined specificity was 0.92 (95% CI, 0.88 to 0.95). Overall, the positive and negative predictive values of MRSA colonization were 0.19 (95% CI, 0.11 to 0.26) and 0.98 (95% CI, 0.92 to 1.0)

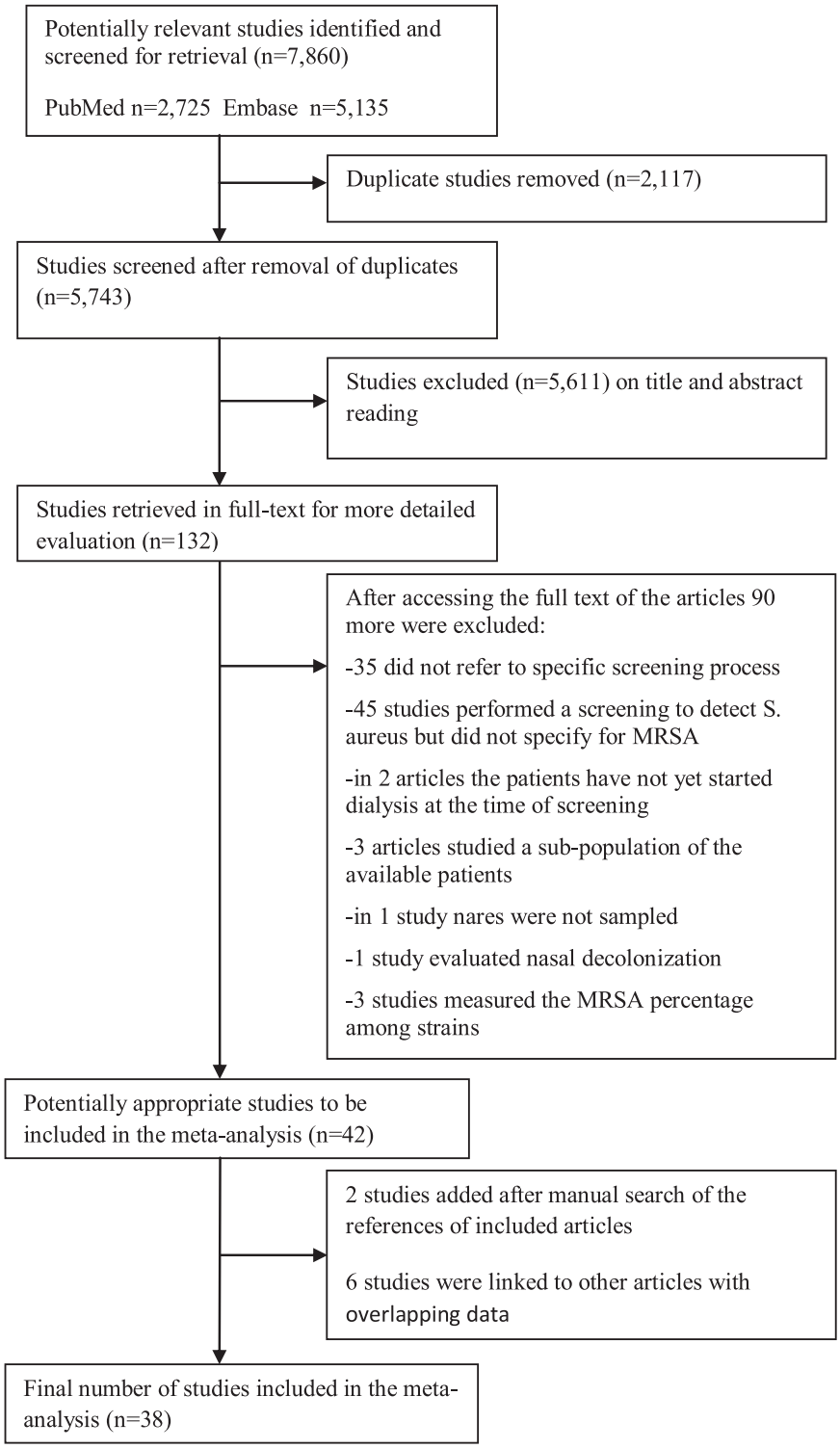

Figure 1. Flow diagram of meta-analysis. Number of studies screened, assessed for eligibility, and included in the meta-analysis with reasons for exclusion at each stage.

respectively, for prior probabilities of infection ranging from 1.9% to 4.7%. Taken together, these numbers suggest that 19% of hemodialysis patients who are MRSA colonized will develop a MRSA infection within 6–20 months of screening compared with only 2% of noncolonized patients. There were no data to pool for the risk of infection among peritoneal dialysis patients.

DISCUSSION

Bloodstream and other infectious complications are a leading cause of death among individuals requiring chronic dialysis and MRSA is one of the major pathogens that cause infections in this population.[53] The purpose of this study was to investigate the significance of MRSA colonization among patients on dialysis, estimate the prevalence of MRSA colonization in this population, and measure the effect of this colonization on MRSA infections. The overall prevalence of MRSA colonization in this patient population was 6.2%, has increased over time, and seems to have stabilized after 2000. Interestingly, the prevalence among hospitalized patients was 3 times higher than among outpatients. In addition, we stratified the patients according to the modality of dialysis and found an association between the modality and the prevalence of MRSA colonization (7.2% in hemodialysis patients versus 1.3% in peritoneal dialysis patients). Importantly, we found a relative risk of 11.5 in developing MRSA infections among colonized hemodialysis patients compared with the noncolonized hemodialysis patients. We estimated that the probability of developing a MRSA infection within 6–20 months is 19% among MRSA colonized patients compared with just 2% among hemodialysis patients that are not colonized.

This analysis highlights the high prevalence of MRSA colonization in this population, which is comparable to that reported among other high-risk populations such as critically ill patients in the intensive care unit (ICU).[54] Of note is that the estimated prevalence might underestimate the actual burden of MRSA in dialysis patients, because all studies included in this analysis used culture to screen for MRSA colonization, which has lower sensitivity compared with PCR that is now frequently used.[55] Interestingly, our study indicates that MRSA colonization in dialysis patients has increased over time, similar to patients in the ICU.[54] The trend seems to stabilize after 2000, a result that

Table 1. Characteristics of eligible studies

Study	Index Year	Location	Screening[a]	Outpatient or Inpatient	Type of Dialysis (HD, PD, or Both)	Screening Sites	Evaluable Sample, *n*	MRSA Colonized, %
Europe								
Celik G[15]	2010	Turkey	Multiple, two positives	Outpatient	HD	N	184	4.9
Schmid H[16]	2007	Germany	Multiple, single positive	Outpatient	HD	N	289	11.8
Bogut A,[13,17]	2004	Poland	Once	Inpatient	HD	N, V	43	2.3
Lederer SR[18]	2004	Germany	Multiple, single positive	Outpatient	HD	N	136	11.8
Duran N[19]	2004	Turkey	Once	Outpatient	HD	N	261	20.7
Mountricha A[20]	2004	Greece	<24 h	Inpatient	HD	N	9	33.3
	2004	Greece	Once	Outpatient	HD	N	41	2.4
Koziol-Montewka[21]	2004	Poland	Once	Outpatient	HD	N	43	2.3
Peña C[22]	2000	Spain	Multiple, single positive	Outpatient	HD	N	71	4.2
Nouwen JL[23]	1998	Netherlands	Multiple, single positive	Outpatient	PD	N, C	52	0
Nouwen J[24]	1996	Netherlands	Multiple, single positive	Outpatient	PD	N, C	98	0
Kluytmans JA[25]	1992	Netherlands	Multiple, single positive	Outpatient	HD	N	174	0
Boelaert JR[26]	1990	Belgium	Multiple, two positives	Outpatient	HD	N	150	0
Oh J[27]	NR	Northern Europe	Multiple, single positive	Outpatient	PD	N	92	2.2
Aktaş E[28]	NR	Turkey	Multiple, two positives	Outpatient	HD	N, A, P	30	3.3
	NR	Turkey	Multiple, two positives	Outpatient	PD	N, A, P	40	0
Cavdar C[10,11,29]	NR	Turkey	Multiple, single positive	Outpatient	PD	N, A, G, C	36	0
North America								
Patel G[30]	2007	United States	Multiple, single positive	Outpatient	HD	N, A, V	102	16.7
Alexander EL[31]	2007	United States	Once	Outpatient	HD	N	157	6.4
Mermel LA[32]	2006	United States	Once	Outpatient	HD	N	208	14.9
Johnson LB[33]	2006	United States	<3 d of admission	Inpatient	Both	N	120	21.7
Pop-Vicas A[34]	2005	United States	Once	Outpatient	HD	N	67	4.5
Vas SI[14,35]	1998	Canada	Once	Outpatient	PD	N, A, G, C	167	1.2
Kirmani N[36]	1978	United States	Once	Outpatient	HD	N, T, S	50	0
Watanakunakorn C[37]	NR	United States	Multiple, single positive	Outpatient	HD	N	52	0
Hadley AC[38]	NR	United States	Once	Outpatient	HD	N, C	197	5.6 (5.6)[b]
Holton DL[39]	NR	Canada	Multiple, two positives	Outpatient	HD	N	68	1.5
Berman DS[40]	NR	United States	Once	Outpatient	HD	N, T, S	54	9.3
Price[41]	NR	United States	<48 h	Inpatient	Both	N	118	11.0
Asia								
Kang YC[42]	2011	Taiwan	Once	Outpatient	HD	N	116	5.2
	2011	Taiwan	Once	Outpatient	HD	N	129	2.3
Yeoh LY[43]	2010	Singapore	≤24 h of admission	Inpatient	HD	N, A, G, W	179	15.1
Uehara Y[44]	2009	Japan	Once	Outpatient	HD	N	112	8.9
Wang CY[12,45]	2007	Taiwan	Once	Outpatient	HD	N	541	5.9
Lai CF[46]	2007	Taiwan	Multiple, single positive	Outpatient	HD	N	306	9.5
Ghasemian R[47]	2006	Iran	Once	Outpatient	HD	N	84	27.4
Lu PL[48]	2002	Taiwan	Multiple, single positive	Outpatient	HD	N	509	2.4
	2002	Taiwan	Multiple, single positive	Outpatient	PD	N	83	2.4
Saxena AK[9,49]	1998	Saudi Arabia	Multiple, two positives	Outpatient	HD	N	208	9.6
Aminzadeh Z[50]	NR	Iran	Once	Outpatient	HD	N	96	45.8
Africa								
Oumokhtar B[51]	2010	Morocco	Once	Outpatient	HD	N	70	1.4
Souly K[52]	2008	Morocco	Multiple, single positive	Outpatient	HD	N	54	5.6

Data are stratified by location and mid-year of each study. HD, hemodialysis; PD, peritoneal dialysis; N, nose; V, vascular access site; C, catheter exit site; NR, not reported; A, axillae; P, perineum; G, groin; T, throat; S, skin; W, wound.

[a]Once: screening was performed once. Multiple, single positive: multiple screenings were performed; one positive result was enough for a patient to be considered a carrier. Multiple, two positives: multiple screenings were performed; two positive results were needed for a patient to be considered a carrier. In hospitalized patients, the time from admission to screening is reported.

[b]Data on nasal colonization are in parentheses.

Table 2. Summary estimates of included studies

MRSA Colonization	Studies (Stratified Data Sets), *n*	Patients at Risk, *n*	Combined Prevalence, % (95% CI)	τ^2	*P* Value
All studies	38 (42)	5596	6.2 (4.2 to 8.5)	0.072	
Screening site					
Nares only	26 (29)	4428	7.1 (4.6 to 10.0)	0.072	Ref
Nares plus additional sites	12 (13)	1168	4.4 (1.6 to 8.6)	0.083	0.28
Geographic region					
United States	10 (10)	1125	7.9 (4.4 to 12.3)	0.045	Ref
Europe	15 (17)	1749	4.0 (1.5 to 7.7)	0.096	0.19
Asia	9 (11)	2363	10.3 (5.7 to 16.0)	0.077	0.51
Type of dialysis					
Hemodialysis	31 (33)	4790	7.2 (4.9 to 9.9)	0.069	Ref
Peritoneal dialysis	7 (7)	568	1.3 (0.5 to 2.4)	0.00	0.01
Setting					
Inpatient	5 (5)	469	14.2 (8.0 to 21.8)	0.034	Ref
Outpatient	34 (37)	5127	5.4 (3.5 to 7.7)	0.070	0.04
Screening of outpatients[a]					
Once	16 (17)	2393	8.2 (4.6 to 12.7)	0.087	Ref
Multiple (single positive)[b]	13 (14)	2054	3.8 (1.7 to 6.6)	0.051	0.07
Multiple (two positives)[c]	5 (6)	680	3.0 (0.6 to 7.3)	0.049	0.10

Ref, referent subgroup for comparison
[a]All inpatients were screened once for MRSA.
[b]Multiple screenings were performed per patient, but only one positive result was needed to define a carrier.
[c]Multiple screenings were performed per patient, but two positive results were needed to define a carrier.

is in line with the relatively stable, and in some studies decreasing, trend of nasal carriage among healthy individuals and non-ICU hospitalized patients.[56,57]

MRSA colonization is significantly higher among hospitalized patients on dialysis compared with outpatients (14.2% versus 5.4%), indicating that the contact with the hospital environment plays a significant role in the colonization of the dialysis patients. This is not surprising because the rehospitalization rate in this population within 30 days is as high as 36%.[53] In addition, hospitalized patients may differ from outpatients in many ways, such as comorbidities and exposure to antibiotics. Interestingly, the prevalence of MRSA colonization in our analysis varied significantly between hemodialysis and peritoneal dialysis patients (7.2% versus 1.3% respectively). This difference could be a result of the difference in comorbidities between the two patient populations. For example, Miskulin *et al.* report that the number of comorbidities of ESRD patients, before the onset of dialysis treatment, was significantly lower in patients who later started peritoneal dialysis, and this was independent of other factors that could influence the modality selection.[58] The difference in comorbidities and the fact that hemodialysis requires frequent contact between patients and the health care system could explain the transmission of antibiotic-resistant pathogens.

Remarkably, we estimated that 19% of MRSA colonized hemodialysis patients would develop a MRSA infection in the following 6–20 months compared with only 2% of noncolonized hemodialysis patients, and the risk of developing an MRSA infection in this population is 11.5 times higher among patients who are MRSA colonized compared with patients that are not colonized. This finding is current because it is based on four different studies published after 2011.[28,30,42,46] The high long-term risk of MRSA infection among colonized patients has also been demonstrated among hospitalized patients (another high-risk population), in which Datta *et al.* showed that 23% of hospitalized patients who were MRSA carriers developed a MRSA infection during the following year.[59] It is encouraging that even with this stable trend in colonization after 2000 and the fact that MRSA colonization is closely associated with infection,[60] the rate of MRSA infections among dialysis patients in the United States over the last 8 years has been declining.[61,62] This decrease in the infection rate seems to be multifactorial and correlates with the decreasing use of central venous catheters (CVCs) as a vascular access for dialysis (nine reporting areas in the United States showed a consistent reduction in the proportion of hemodialysis patients with a CVC from 27.8% in 2005 to 18.8% in 2011)[61] and the use of aseptic techniques for catheter insertion and maintenance.[63] These interventions (decreasing use of CVCs and improved aseptic techniques) seem to reduce the risk of infection in both colonized and noncolonized patients and along with the strict compliance to infection control policies (including the possible increase in the use of decolonization methods) may further decrease the infection rate in the future.

Of note is that the risk of developing MRSA infection among colonized patients can be affected by several factors that may be specific to the particular patient, provider, or facility (*e.g.*, comorbidities, use of antibiotics for prophylaxis or treatment, and infection control practices). These factors may also

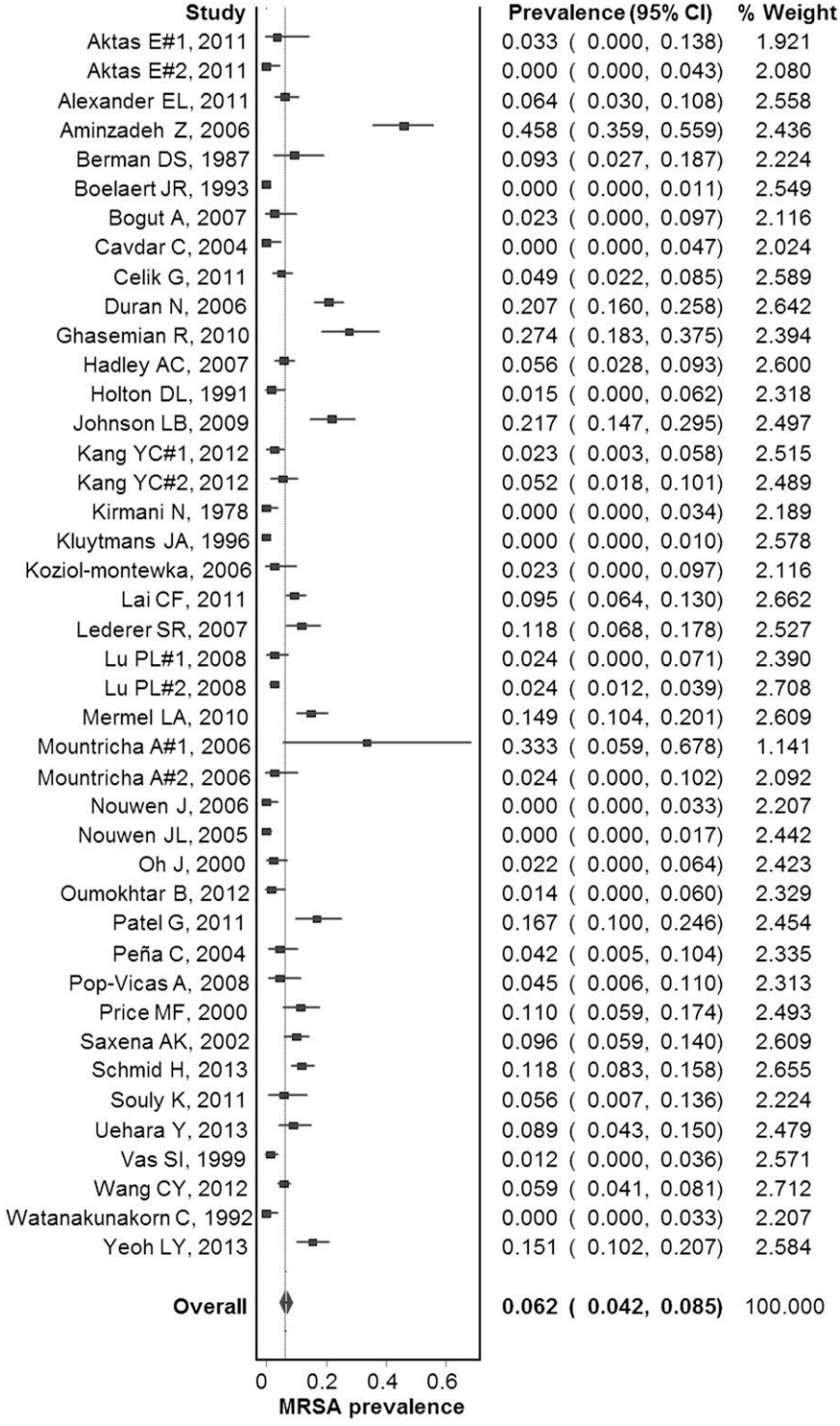

Figure 2. Forest plot of included studies. Individual and combined estimates of prevalence of MRSA colonization.

change significantly over time and may be very different in different parts of the world. Our estimated risk of infection combines the risk from different settings, patient populations, and healthcare practices and may not apply to a specific center where local epidemiology, infection control policies, and patients' characteristics may affect MRSA infection. The method used for culture (*e.g.*, chromogenic media, nonchromogenic selective media, or enrichment broth) as well as the sites screened in each study can have a significant effect on the detection of MRSA, and can represent an additional source of heterogeneity.[64,65] However, we were not able to show a significant difference of MRSA prevalence based on the screening strategy (nasal or nasal plus extranasal site screening). Nevertheless, our findings provide an important overall estimation and they are based on recently published studies.

In addition to chronic or persistent MRSA colonization, there are also intermittent carriers.[66] We cannot be sure that patients were persistently colonized during the 6–20 months of follow-up until they developed the MRSA infection and there is the theoretical possibility that these patients lost and reacquired MRSA close to their infection.[67–69] In addition, because different studies had different follow-up periods, we were unable to determine the exact risk of infection over time. By summarizing the reported effect of MRSA colonization in the development of MRSA infection, we highlighted the importance of colonization in this population and provided an estimation of risk of infection over 6–20 months (the duration of follow-up observation in the studies included in our meta-analysis).

Our data underscore the association of MRSA colonization with MRSA infections. Implementing a uniform policy for managing MRSA colonization is challenging, given the unique characteristics of the dialysis population (frequent contact with the health care system, long duration of dialysis treatment, and high frequency of hospitalizations), which raise the concerns of recolonization[70] and of the emergence of mupirocin-resistant strains.[71,72] However, the MRSA colonization rate among dialysis patients is approximately 6.2% and it is associated with an 11.5-fold increase in the risk of MRSA infections among hemodialysis patients. Overall, one-fifth of colonized hemodialysis patients will develop a MRSA infection during the following 6–20 months. Because invasive MRSA infection is associated with a >30% mortality,[1] there is a need for strict compliance with the recommendations of the US Centers for Disease

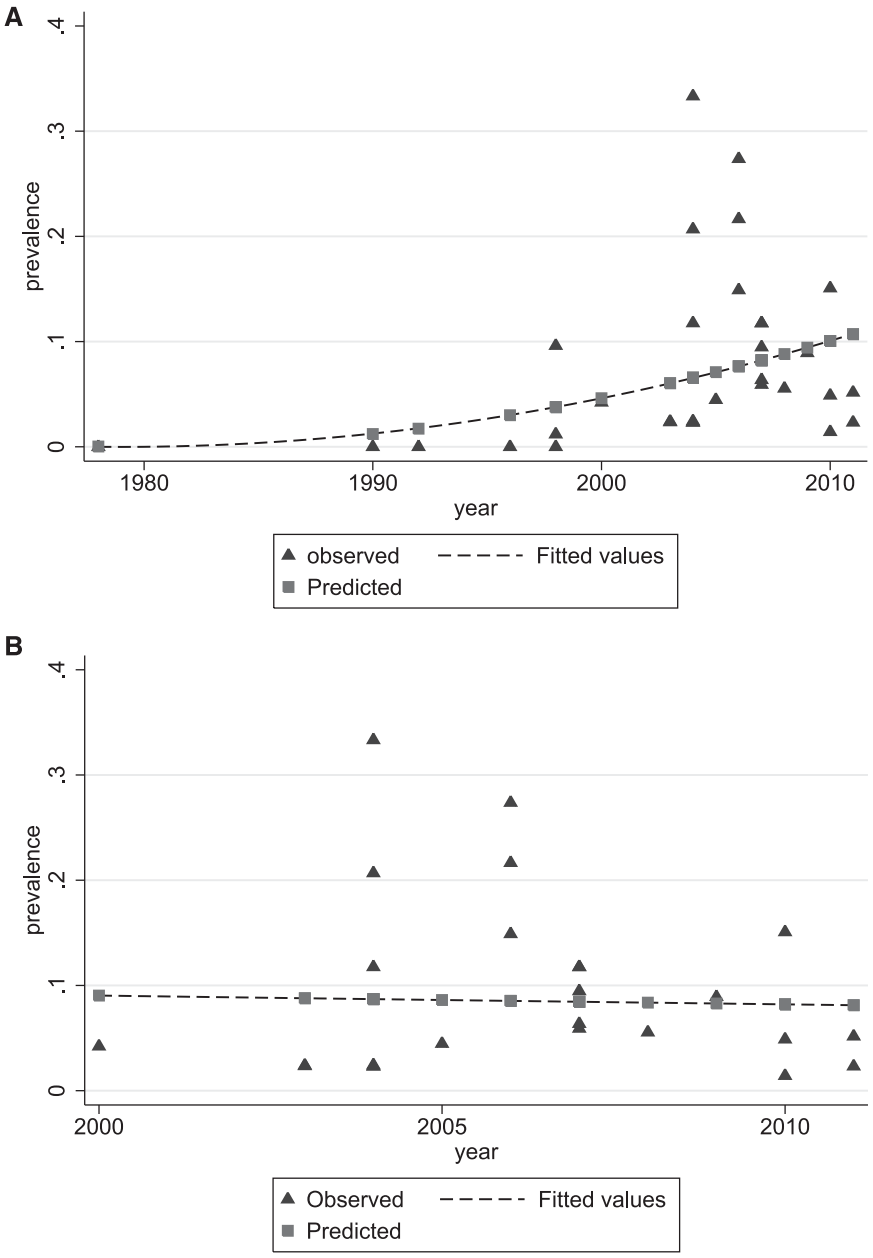

Figure 3. MRSA colonization trends over time. (A) Observed (triangles) and fitted (dashed line) MRSA prevalence estimates (all studies), by study mid-year. (B) Observed (triangles) and fitted (dashed line) MRSA prevalence estimates, by study mid-year, for studies conducted after 2000.

Control and Prevention and National Kidney Foundation[73,74] and for a systematic effort to combat MRSA colonization in this population.

CONCISE METHODS

Study Selection

We performed a PubMed and Embase literature search to identify all studies on MRSA colonization among patients undergoing dialysis treatment. The search terms were as follows: (MRSA OR *Staphylococcus* OR (methicillin AND resistant)) AND (dialysis OR hemodialysis OR peritoneal). Retrieved citations were reviewed by title and abstract and all potentially relevant studies were accessed in full text. The search was complemented by scanning the reference lists of all included articles. A restriction for English literature was imposed. We did not consider abstracts, conference proceedings, and unpublished material. This meta-analysis follows the Meta-Analysis of Observational Studies in Epidemiology guidelines.[75]

Inclusion and Exclusion Criteria

Studies were included in the meta-analysis if they reported prevalence data on MRSA nasal colonization among individuals with ESRD who had been undergoing regular dialysis treatment. Because *S. aureus* primarily colonizes the nares,[57,66,76] we did not include studies in which nares were not sampled. Many studies provide evidence that MRSA colonization rates are not equally distributed among different groups of dialysis patients.[77] For this, we excluded studies that focused on a specific subpopulation of the available dialysis patients (*e.g.*, studies that included only individuals aged≥65 years, patients with diabetes, *etc.*). We also excluded studies that evaluated colonization rates after implementing nasal decolonization protocols.

Table 3. Individual hemodialysis study data included in the diagnostic meta-analysis

Study	Country	Screening	Follow-Up Period	TP	FP	TN	FN	Sensitivity	Specificity
Kang YC[42]	Taiwan	N	6 mo	1	10	149	1	0.50 (0.01–0.99)	0.94 (0.89–0.97)
Aktaş E[28]	Turkey	N, A, P	6 mo	1	0	29	0	1.00 (0.03–1.00)	1.00 (0.88–1.00)
Lai CF[46]	Taiwan	N	613 d	5	24	271	6	0.45 (0.17–0.77)	0.92 (0.88–0.95)
Patel G[30]	United States	N, A, V	12 mo	3	14	84	1	0.75 (0.19–0.99)	0.86 (0.77–0.92)

All studies used culture methods to identify MRSA. TP, true positive; FP, false positive; TN, true negative; FN, false negative; N, nasal; A, axilla; P, perineum; V, vascular access site.

Outcomes of Interest

The primary outcome of interest was the prevalence of MRSA nasal colonization among dialysis patients. Prevalence was calculated as the proportion of patients with a positive screening result among the patients "at risk" (*i.e.,* those that were screened for MRSA colonization). Effects were adjusted for geographical region, dialysis modality (hemodialysis versus peritoneal dialysis), dialysis setting (inpatient versus outpatient), and sampling process (nasal versus nasal and extranasal sampling, one-time screening versus multiple screenings). The secondary outcome of interest was the relative risk of colonized patients compared with noncolonized patients to acquire a MRSA infection.

Data Extraction

Using standardized forms, two reviewers (I.M.Z., F.N.Z.) independently extracted relevant information from the text, tables, and figures of eligible articles. Extrapolated information of included articles was summarized using a spreadsheet. Data from trials published in duplicate were included only once, and the maximum of relevant information was extracted. Consensus was reached if there were any discrepancies between the reviewers.

The following data were extracted. First, we extracted the characteristics of each study, including the study design (prospective versus retrospective), the country of origin, and the study period. Second, information on the patient population, including the population screened, the number of MRSA colonized patients, the type of dialysis treatment used (hemodialysis, peritoneal dialysis), and the dialysis setting (inpatient, outpatient) was extracted. Moreover, the details of the screening process, such as the anatomic sites screened (nasal or nasal plus extranasal sites), the method of MRSA isolation (culture or PCR), the definition of carriage state, and the time frame of screening process were extrapolated. Finally, we extracted the information relevant to the follow-up, including the duration of follow-up and the number of MRSA infections.

In order to model the time trends of MRSA colonization among dialysis patients, an index year of each eligible study was determined. For this purpose, we used the year that the study was conducted and not the year of publication. If the study extended for more than 1 calendar year, the year that the sampling took place was assumed to be the index year of the study. If the sampling period lasted over 1 calendar year, a mid-year was calculated. The surveillance period after the initial sampling was not considered.

Quality Assessment

Two reviewers (I.M.Z., F.N.Z.) independently assessed the methodologic quality of eligible studies using the Newcastle-Ottawa Quality Assessment Scale.[78] According to the requirements of the scale, studies received stars in the context of the representativeness of the exposed cohort, ascertainment of exposure, assessment of outcome, adequacy of follow-up time for outcomes to occur, and adequacy of follow-up of cohorts. Included studies could receive a maximum of five stars because the fields "selection of the nonexposed cohort," "demonstration that the outcome of interest was not present at the start of the study," and "comparability between cohorts" were not applicable to our studies. Studies that received at least four stars were deemed of high quality. Details of the quality assessment of all eligible studies are provided in the Supplemental Appendix.

Statistical Analyses

We used the Freeman–Tukey arcsine methodology in order to deal with stabilizing variances.[79] The meta-analysis was performed using a random-effects model to estimate the pooled (combined) prevalence and the 95% CIs, using DerSimonian and Laird weights.[80] Heterogeneity was assessed using the between-study variance τ^2 estimation.[80,81] Egger's test for publication bias was used to address small study effects.[82] Furthermore, we incorporated a subgroup and meta-analysis regression technique to adjust for possible sources of heterogeneity. For time trends, the estimated coefficients were retransformed to prevalence and fitted values were drawn against the index year.[54,83]

To assess the effect of MRSA nasal colonization on MRSA infection among dialysis patients, we performed a diagnostic meta-analysis using a bivariate, mixed-effects binomial regression model to account for within-study and between-study variability.[54,84,85] We followed this methodology because it is considered more suitable when variability beyond the threshold effect is documented.[86,87]

Statistical analysis was performed using the Stata v11 software package (StataCorp, LP, College Station, TX) and MetaXL (EpiGear International, Ltd., QLD, Australia). The MIDAS (Meta-analytical Integration of Diagnostic Accuracy Studies) set of commands in Stata was used to implement the diagnostic meta-analysis.[88,89] The significance threshold was set at 0.05.

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DISCLOSURES

None.

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