Negative-pressure wound therapy for III/IV pressure injuries: a meta-analysis

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Conflict of interest

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Short running title

Negative-pressure wound therapy for pressure injuries.

Key words

III/IV Pressure injuries; Negative-pressure wound therapy; Randomized controlled trial; Meta-analysis

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Abstract

This meta-analysis was conducted to identify the potential benefits and the efficacy of negative-pressure wound therapy (NPWT) for III/IV pressure injuries (PIs) compared with standard wound care (SWC). Sixteen RCTs with 629 patients were included in our analysis. The methodological quality was assessed by Cochrane Collaboration Tool. The outcomes included complete ulcer healing rate, wound healing time, pain score, the frequency of dressing change, hospitalization cost, the condition of the exudate and the wound improvement. The percentage of healing rate was 61.45% for NPWT group and 36.90% for SWC (95% CI: 1.32–1.70). There were significant differences in wound healing time [WMD = -16.47 days, 95% [CI (-22.36, - 10.59) days, $P \leq 0.001$]]. The pain score and hospitalization cost in NPWT was lower compared with SWC group [WMD = -2.39, 95%CI (−3.47, -1.30), $P \leq 0.001$]; [SMD = -2.55, 95%CI (−4.07, -1.03), $P < 0.01$]. The frequency of dressing change in both NPWT groups were greatly reduced [SMD = -3.61, 95% [CI (-4.57, - 2.66) times, $P \leq 0.001$]]. Our meta-analysis indicated that NPWT was associated with greater improvements in improving PIs and shorting healing time for III/IV PIs. However, this conclusion needs to be confirmed by high-quality multicenter RCTs.

Key words III/IV Pressure injuries; Negative-pressure wound therapy; Randomized controlled trial; Meta-analysis

1. Introduction

Clinically, the incidence of pressure injuries (PIs) has increased significantly, greatly affecting the survival rate of patients[1]. Our recent study has indicated that patients complicated with PIs are estimated to have a 2 times higher risk on mortality compared to patients without PIs[2]. The incidence of PIs has increased by 63% in recent years[3]. After debridement, medical dressing is the main treatment, but the infection rate still reaches 10-30%[4]. Therefore, actively looking for more effective methods to treat PIs is a hotspot.

Negative-pressure wound therapy (NPWT) is believed to promote wound healing through a variety of mechanisms, such as draining excess exudate, reducing edema, eliminating barriers to cell proliferation, and thus accelerating the wound healing process[5,6]. Traditional SWC refers to the treatment of chronic wounds with frequent (three to four times daily) saline moist dressings[7]. A number of studies have applied NPWT to the prognosis of wounds of III/IV PIs. The results showed that NPWT had achieved great results in the treatment of III/IV PIs. Some studies claimed that NPWT compared to SWC accelerated wound closure, reduced infection rates, labor and costs[8,9]. A study of a mixed population treated by a family health group showed that NPWT reduced the hospitalization rate of PIs[10]. However, the vacuum machines of NPWT are considerably more expensive than SWC.

In addition, there were still many controversies in the application of NPWT in III/IV PIs. The

reliable evidence supporting the efficacy of NPWT in the treatment of III/IV PIs remains weak and inconsistent[11,12]. For wound healing rate, a recent article suggested that the evidence for using any non-pharmacologic therapy such as NPWT to improve wound healing rate was inconclusive[13]. Some but not much evidence showed that NPWT could reduce the quality of life of patients[14]. For the cost, Kim et al. said that these commercial devices such as NPWT were still expensive, and the financial burden may limit the use of NPWT in budget-constrained environments[15].

What's more, there was a lack of large-sample research evidence regarding its clinical and cost effectiveness. Many articles have explored the application of NPWT in other wounds which compared to SWC, such as in diabetic foot wounds[16,17], closed laparotomy incisions in general and colorectal surgery[18,19], open fractures[20] and other problematic and chronic wounds[21]. However, there is limited evidence among patients with III/IV PIs. Dumville et al. described the efficacy of NPWT and SWC in PIs[22]. Their results showed that there was no strict RCT evidence for the efficacy of NPWT compared to other methods of treating PIs. High uncertainty existed about the efficacy of this treatment. And they did not limit their patients' levels of PIs.

Therefore, we tested the hypothesis that NPWT is superior to SWC in treating stage 3.4 PIs. In light of these conflicting results, we conducted a meta-analysis of all RCTs comparing NPWT with SWC to investigate whether NPWT increased the rate of PIs healing, reduced wound healing time and pain in patients, and improved disease. The aims of this study were to objectively assess the

efficacy and the feasibility of conducting NPWT in curing III/IV PIs and provide a reliable basis for clinical practice.

2. Methods

2.1 Search strategy

Seven databases (PubMed, Cochrane Library, Embase, Web of science, CNKI, WanFang and VIP) were searched up to December of 2019. The Medical terminology (MESH) terms and free text words were used. The search included the following MeSH terms: Pressure Ulcer, Decubitus, Negative-Pressure Wound Therapy, Vacuum Assisted Closure, Suction, Vacuum and Randomized Controlled Trial. All MeSH terms were converted to synonyms that were appropriate for each particular database. Other potentially relevant studies were identified by cross-referencing in eligible studies. The search details for each database were described in the supplemental material (addendum).

2.2 Study selection

The systematic review was restricted to published trials done on human subjects, focusing only on NPWT application for the treatment of PIs, and written in both English and Chinese language. Inclusion and exclusion criteria are shown as followed:

Inclusion criteria: P (population): Patients meet the III or IV PIs diagnostic criteria according to

NPUAP; I (intervention): NPWT devices used for PIs compared with SWC; C (comparison): Any type of the SWC such as moist gauze and various wound dressings; O (outcome): the primary outcomes were the rate of complete healing and PIs healing time; the secondary outcomes were pain score, the time of dressing change, hospitalization cost and the condition of the exudate and the wound improvement. S (study design): only RCTs that compared NPWT with SWC in patients with PIs were selected.

Exclusion criteria: (1) no RCT was performed; (2) no comparison between NPWT and SWC; (3) study did not show corresponding one of the needed outcomes such as the mean, the standard deviation or the RR; (4) multiple intervention measures.

Studies that recruited participants with 3.4 PIs and other types of wounds were included if the results for people with relevant PIs were presented separately.

2.3 Quality assessment and data extraction

Two screening authors independently extracted relevant data according to the eligibility criteria. The third reviewer would be consulted to resolve the disagreements between the two screening authors. Two independent screening authors used the Cochrane Collaboration Tool to independently evaluate random allocation methods, allocation scheme hiding, blinding, completeness of outcome data, reporting bias, and other sources of bias. They discussed the results and reached a consensus. Each project will be rated as ‘low risk of bias’, ‘unclear risk of bias’ or ‘high risk of bias’. If the

information is not sufficient, the relevant authors were contacted to ensure that each item was adequate. RevMan5.2 was used to plot risk of bias. Studies were initially reviewed by title then abstract for relevance before being considered for inclusion and assessed using the eligibility criteria. Interventions and comparators were assumed to be NPWT systems and SWC. They extracted the following information from each included study: first author; publication year and country; study size and the type of treatment (including type of NPWT device, SWC for comparison; outcome measures; case inclusion time; complete ulcer healing rate; follow-up period. If necessary, we will add more information, especially between various NPWT or dressings. We extracted the number of people or wounds from each treatment group and control group. We extracted data on the primary efficacy outcomes, such as the number and timing of wound closure. We add the identified potential problems, such as unclear definitions of PIs healing. We extracted the measurement results of the treatment group and the control group, including mean, standard deviation and incidence.

2.4 Outcome measures

The primary outcomes were the rate of complete healing and the wound healing time. The complete healing rate of the PIs was defined as granulation tissue growth or discontinuation of treatment to achieve healing. The wound healing time was defined as a complex combination of regeneration of various tissues and granulation tissue proliferation and scar tissue formation, showing synergy of various processes.

The secondary outcomes included the pain situation (It was defined as methods using VAS and the like), dressing change workload (It was defined as the frequency of dressing change or the total number of dressings during the trial period), the hospitalization cost (It was defined as all the expenses including nurse care and others spent on hospitalization during treatment) and the condition of the exudate and the wound improvement.

Studies if their primary outcome measures are not ulcer healing defined in this meta-analysis would be excluded.

2.5 Statistical method

In this study, meta-analysis of categorical variable and continuous variables were performed by using the STATA SE 11 software. The continuous variables included wound healing time, pain score, time of dressing change, hospital costs, the condition of the exudate and wound improvement. The categorical variable was healing rate. The weighted mean difference (WMD) with 95% confidence interval (95%CI) was calculated by using the mean and standard deviation for continuous variables. SMD was used to calculate the continuity variables with different unit and a large difference in mean. SMD was used because the statistical units of the frequency of treatments included in the articles were different. A fixed-effect model was used if the heterogeneity test did not show statistical significance ($I^2 < 50\%$, $P > 0.1$) [23,24]. Risk Ratio (RR) was entered for the dichotomous data. Funnel plot was used to assess the publication bias[25]. Sensitivity analysis generally is used to check if

analysis results are robust if assumptions of analysis are changed. A subgroup analysis was conducted based on the definition of wound healing. $P < 0.05$ was considered to be statistically significant. Descriptive analysis was conducted if the heterogeneity was too obvious to determine the source and the evaluation result were not unified.

3 Results

3.1 Study selection and study characteristics

On the basis of a review of database searches of 412 articles we assessed 33 full-text articles for eligibility. 17 studies were excluded for the following reasons: did not meet inclusion criteria (n=5); not an RCT (n=4); did not describe PIs (n=4); did not compare with SWC (n=2); review or case (n=2). Sixteen studies [26-41] which published from 2002 to 2017 matched the eligibility criteria and were included in the final qualitative study. All the studies consistently reported positive effects of NPWT application. Fig.1 showed the search strategy yielded a total of 16 articles for the meta-analysis.

The 16 RCTs included 629 patients. The table.1 showed the basic characteristics of the included studies. The studies selected for inclusion included one from the US, two from India, one from UK and twelve from China. The included studies achieved randomisation of participants in a variety of ways. One of the included studies used pre-generated permuted blocks (A computer-generated code

with random, permuted blocks was used to assign treatment. The block sizes of four and six) [42]; three studies used computer-generated random table[28,29,33]; one study used coin-tossing[39]; one study using simple sampling[34] and ten studies only referred to randomization but did not explain specific methods. Control and test groups were comparable in all included studies.

3.2 Risk of bias assessment

The risk of bias of the included studies was showed in Fig. 2. Four studies described the randomized methods. Low-level articles were mainly caused by incorrect random distribution and blinding. No study mentioned blind allocations. All the studies' outcomes were complete.

3.3 The primary outcomes

Complete ulcer healing rate

Eight RCTs reported the data on the healing rate of PIs for the effect of NPWT and SWC[29,30,34,35,37-39,43]. The healing rate in the NPWT group was 61.54% and in the standard treatment group was 36.90%. The use of NPWT was associated with increase in the risk of the healing rate of PIs in patients compared with SWC (RR=1.32; 95% CI 1.32–1.70). There was no statistical heterogeneity among the evaluated trials (I^2=0.0%, P =0.492) (Fig. 3a). Compared with SWC, the RR value of the NPWT group in China is 1.46 (95% CI 1.05-2.03; I^2=6.9%; P=0.373)(Fig. 3b). Sensitivity analysis showed the result was robust (Fig. 3c). Articles of Ali[26] and Wang[39] were the sources of heterogeneity.

Wound healing time

Ten RCTs provided the data for the effect of NPWT and SWC on the healing time of PIs[30,32,34-41]. Meta–analysis about the comparisons of the difference from pre- to post-intervention between NPWT and SWC revealed a statistically significant moderate effect size [WMD = -16.47 days, 95% [CI (-22.36, - 10.59) days, $P \leq 0.001$; see Fig. 4a]]. Strong evidence of heterogeneity was observed (I^2=98.2%, $P \leq 0.0001$). The funnel plot showed the evidence of publication bias based on the ten RCTs (Fig.4b). Sensitivity analysis showed the result is robust. No significant changes were observed in the results of any studies removed (Fig.4c). Two articles did not mention the concept of wound healing, four articles indicated that the growth of fresh granulation was considered as healing, and four articles defined the concept of wound healing as complete scab healing. Subgroups were selected based on the definition of wound healing [WMD = -17.42 days, 95% [CI (-25.87, - 8.97) days, $P \leq 0.001$; WMD = -6.39 days, 95% [CI (-8.65, -4.14) days, P =0.536]] (Fig.4d).

3.4 The secondary outcomes

Pain of III/IV PIs

There studies [37,38,41] were included in this analysis of the pain score of NPWT versus SWC. Strong evidence of heterogeneity was found by random effect model analysis (I^2 = 93.5%) (Fig.5). All three analyses showed that the use of NPWT showed to be a significant advantage that relieved the pain in hospital [WMD = -2.39, 95%CI (−3.47, -1.30), $P \leq 0.0001$].

Dressing change workload

Eight RCTs[27,34-38,40,41] provided the data for the effect of the time of dressing change during the trail. Meta-analysis about the comparison revealed a statistically significant effect respectively [SMD = -3.61, 95% [CI (-4.57, - 2.66), $P \leq 0.001$; see Fig. 6a]. Strong evidence of heterogeneity was found by random effect model analysis (I^2 = 85.4%). In China the data for the effect of the time of dressing change during the trails showed that the SMD =-3.82 (-4.85, -2.78) (I^2=86.7%; $P \leq 0.001$) (Fig. 6b).Sensitivity analysis showed the result is robust (Fig.6c).

Hospital costs

Three studies [31,33,40] on hospitalization cost of NPWT was significantly different compared with SWC group [SMD = -2.55, 95%CI (−4.07, -1.03), P <0.01] (Fig.7a). Sensitivity analysis showed the result was robust (Fig.7b).

The condition of the exudate

Two articles [28,32] evaluated the condition of the exudate. Since the evaluation results were not unified, we used descriptive analysis. Hong[32] et al. showed that the ratio of exudate in the NPWT group was 29.41% and 75% in the first week and the second week, respectively, and their proportion was smaller than the SWC group. Dwivedi et al.'s study[28] reported exudate levels at the sixth and ninth weeks. The data showed that the mean and standard deviation (1.52±0.68, 0.14±0.35) in the NPWT group were smaller than the mean and standard deviation (2.17±0.49, 1.35±0.75) in the SWC

group.

The condition of the wound improvement

Three articles evaluated the improvement of PIs including ulcer volume reduction rate, wound reduction rate and the length, width and height of PIs. Ford and Ali et al. mentioned that the volume reduction rate of PIs in the NPWT group (57% and 56.7%) was greater than that in the SWC group (25% and 30%). Ali et al. also reported a reduction in 90% of wounds in the NPWT group during the follow-up, compared with only 63.33% of the wounds in the SWC group. Dwivedi et al. showed that the height, width and depth of the wounds in the NPWT group were significantly lower than those in the SWC group (length: week-6: 3.05±1.99, 4.23±1.87; week-9: 1.52±1.66, 3.24±1.65; width: week-6: 2.57±2.12, 3.51±1.64; week-9: 1.19±1.33, 2.55±1.72; depth: week-6: 1.84±1.51, 1.95±0.56; week-9: 1.19±1.33, 1.16± 0.5).

4. Discussion

The results of this study showed that treatment with NPWT was associated with increased the healing rate (RR=1.32), shorter the wound healing time (WMD = -16.47days), decreased patients' financial burden and suffering and workload of medical staff compared with SWC. III/IV PIs are prone to cause infections due to environmental and patients' factors in routine treatment. III/IV PIs are a growing challenge for both the clinician and the patients[44-46]. A study was conducted on 114 patients with PIs over 50 years old and the results showed that the healing rate of PIs was only 10.5%

(12/114) within three months. The healing rate of the 4 PI was as low as 2.6%[47]. Standard wound care (SWC) of dressings and debridement for III/IV PIs treat the patient for a long time with poor efficacy. They may lead to additional complications and increase socio-economic burden[48]. NPWT has been applied in other aspects such as diabetic foot ulcers, wound infections and complications after total knee arthroplasty, wound flaps for closed grafts and so on. It has been proposed as a gold standard for the treatment of wounds, such as dehisced sterna wounds[49], abdominal wounds[50] and difficult-to-heal wounds[51]. In our study, NPWT could effectively reduce wound healing time. A similar result was observed in NPWT outcome trial assessing another a diabetic foot ulcers[52] which said that 14.3% of patients with NPWT(43.2%) had complete ulcer closure in less median time compared with controlled group (28.9%). In addition, NPWT significantly reduced surgical site infection rates (pooled OR= 0.16; $P < .001$) and the application of NPWT in closed laparotomy in general and colorectal surgery was similar to that of conventional dressing in the rate of serum swelling and wound dehiscence[19]. Compared with our study， the study of Hyldig et al. assessed the incidence of wound infection (RR=0.54) and seroma (RR=0.48) when applied NPWT to closed surgical wounds and found that NPWT was significantly effective[53]. Studies [48,54] suggested that NPWT had been shown to rapidly reduce wound surface area and volume, especially for deep wounds such as PIs. De Laat et al. also showed that partial negative pressure causes wound healing to be twice as fast as treatment with sodium hypochlorite and was safe for patients with wounds

which were difficult to heal such as III/IV PIs[55]. These results well explained why the application of NPWT was beneficial for the healing of III/IV PIs.

Our study showed that patients in the NPWT group had better healing trend in PIs than in the SWC group. However, the definition of wound healing differs in the included articles. Wang[39], Shen[37], Liu[36] and Liu[35] defined PIs healing as the growth of granulation tissue and epithelialization; Li[34], Su[38], Guo[30], Zhang's[40] study indicated that the wound surface was scabbed completely, which was considered as healing; Hong[32] and Zhou's[41] articles didn't not mention the definition of healing. Different definitions may lead to high heterogeneity in the data. Regardless of the definition, our study showed that the efficacy of the NPWT group was better than that of the SWC group. In addition, the number of healing in the Ford[29], Li[34], and Liu[35] articles referred to the number of wounds healed and the other articles referred to the number of people healed. This can lead to heterogeneity. There are many articles on the healing time of PIs in China, but few abroad. PIs are a significant health care issue and their impact on the individuals is profound which can interfere with the physical, psychological and social health of the patient and affect the quality of life[56,57]. The quality of the articles we included regarding the duration of PIs healing was poor, the high uncertainty of healing and the long follow-up time may lead to unreliable results. Current findings also suggested that patients with NPWT have a reduced pain level, which may be related to a reduction in the number of treatments. However, one study has shown that patients' quality of life

decreased during the first week of using NPWT. This may be related to the patient's pain[14]. This suggested that the patient's pain level may be higher during the first week of treatment. In future research we should analyze the patient's pain level in stages respectively.

Our study still concluded that NPWT could reduce the financial burden of patients. There were studies reported that NWPT was cost-effective compared to SWC and provided minimal discharge and soiling of bed sheets because of the vacuum seal [58,59]. But the hospitalization cost included the care cost, other treatment, and some basic expenses. This may lead to the bias in our results. In the course of this study, we found that many hospitals were trying to use the modified NPWT. They simplify the materials and appliances to greatly reduce the cost of treatment. Compared with NPWT, the modified NPWT greatly reduced hospitalization cost and socioeconomic cost in Wu's 64study. Modified NPWT may prove to be a cost-effective tool in the reduction of treatment cost. However, modified NPWT still lacks corresponding research. We can compare the differences between NPWT and modified NPWT in our future studies. However, there are some doubts about the cost-effectiveness formation. One study showed that NPWT has a low probability of cost-effectiveness in patients with open lower limb fractures[60]. NPWT cannot provide clinical or economic benefits to them. The British PIs Guidelines do not recommend providing conventional negative pressure wound therapy to treat PIs, unless it is used in patients with a large number of wounds[61].

Limitations of this study: (1) The findings were based on a small number of events and the quality of the studies was low, so the statistical power was weak. Subjective factors had a great impact in the process of quality evaluation. The true effect may be close to the estimate of the effect, despite the possibility of substantial differences. (2) There was moderate heterogeneity between the included studies. Independent studies may increase the risk of heterogeneity because of the heterogeneous design of the different studies. The heterogeneity may also come from different definitions of outcomes, age, insufficient method details and follow-up time. (3) There may be publication bias because we only searched the Chinese and English databases. Insufficient randomization and hidden allocation may lead to overestimation of treatment outcomes and measurement bias.

5. Conclusion

Our study showed that NPWT was effective for the treatment of III/IV PIs which included raising the complete ulcer healing rate, reducing wound healing time for III/IV PIs. Meanwhile, NPWT can also reduce the pain in patients, medical staff's workload and patients' treatment cost. We recommend the use of NPWT for the treatment of III/IV PIs in the clinic and financial savings should be recommended. However, the conclusion of the study needs to be confirmed by high-quality multicenter RCTs.

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Reference year	Case inclusion time	Country	Study size		Treatment		Location of PIs	Outcome measures	The stage of PIs	Evaluation time	Treatment time	Age		Follow-up time	Dressings were changed		Complete ulcer healing rate(%)(T/C)
			T	C	T	C						T	C		T	C	
He YF.20[illegible]3	NR	China	20	15	NPWT	SWC	(1)(5)(6)	(1)the wound healing time (2)workload (3)costs	Ⅲ/Ⅳ	NR	NR	NR		NR	NR	NR	NR

Ford,2002	NR	The United States	20	15	VAC	SWC	(1)(3)(4)(6)	(1)rate of wound volume loss (2)PMNs, lymphocytes, capillaries per high-power field (HPF) (3)wound dimensions (4)number of PIs healed	Ⅲ/Ⅳ	6-week	6-week	41.7	54.4	from 3 to 10 months	every monday, wednesday and friday	changed once or twice daily	10/13.3

								(5)cases of disease improvement									
Ali, 2015	February 2014 and March 2015	India	30	30	VAC	dressing	NP	(1) rate of wound volume loss (2)discharge rate (3) number of granulation tissue appeared	Ⅱ/Ⅲ	7-week	2–7 weeks	56	52	the wound closed spontaneously, surgically or until	every 48 to 72 h or sooner if the wound	every 48 to 72 h or sooner	83.3/66.7

								(4)the size decreased						completion of the 50-day period	was infected.		
Rebecca L Ashby,2012	1 September 2008 until 31 August 2009	UK	6	6	NPWT	SWC	(1)	(1)the wound healing time (2)PIs recruitment rates (3)frequency of treatment visits (4)resources used (5)duration of	Ⅲ/Ⅳ	6 months	NR	67.5		6 months	mean ± SD = 25 ± 23;	mean ± SD = 113 ± 5;	NR

								follow-up								
Dwivedi, M. K.2017	NR	India	32	28	NPWT	SWC	NR	(1)exudate levels (2)levels of MMP-8 (3)length, width, and depth of PU (4)granulation tissue	Ⅲ/Ⅳ	3,6,9 week	9-week	53.5 ± 12.5	54.3 ± 14.3	the wound was closed spontaneously or completion of 9 weeks of treatment	every 7 days	once or twice daily	NR
Hu, K. X.2009	From September 2005	China	35	32	NPWT	SWC	NR	(1)treatment time (2)the number of surgery (3)cost	NR	to cure	to cure	45 ± 20	49 ± 17	NR	every 2 ~ 6 days	every 1-2 days	NR

	to November 2008																
Zheng Li,2009	January 2006 to September 2008	China	9	9	VAC	SWC	(1)	(1) the wound healing time (2) the number of treatment (3) workload	Ⅲ/Ⅳ	4-week	4-week	21-82	20-84	NR	every 2~3d once	once a day	68.2/10
Xin-Yuan Shen 2015	June 2012 to Septemb	China	37	37	Modified NPWT	SWC	(1)	(1) the wound healing time (2) the number of	Ⅲ/Ⅳ	10-day	10-day	59.26	57．98 ±2．37	NR	NR	NR	59.5/35.1

	er 2014							treatment (3) wound bacterial culture results				±2. 58					
Qing-Hua Hong,2016	2013 to 2015	China	17	16	NPWT	SWC	NR	(1) the wound healing time	Ⅲ/Ⅳ	0,1,2-week	NR	72.35±4.23	72.63±5,12	NR	every 7 days	every day or every other day	NR
Yi-Fang Su,2012	July 2008 to	China	25	25	Modified	SWC	NR	(1) the wound healing time	Ⅲ/Ⅳ	NR	NR	58．0±5．0		NR	every 2~3d	NR	64/24

	July 2011				NPWT			(2) patient's wound pain score (3) workload						once		
Hong Wang,2012	January 2010 to June 2012	China	18	12	NPWT	SWC	(1)(2)	the wound healing time	Ⅳ	NR	NR	55 ±11.2	56±11.1	NR	5~7d	2 ~ 3 times a day	94.4/91.7
Yan Liu,2016	January 2011 to February 2014	China	10	10	VSD	SWC	(1)(3) (4)	(1) the wound healing time (2) the number of treatment	Ⅲ/Ⅳ	NR	NR	64 ± 12.8	60± 14.8	NR	NR	every day or every other day	NR

								(3) hospitalization costs (4) duration in hospital									
Pei-Fen Guo, 2013	May 2010 to October 2011	China	10	10	VSD	SWC	(1) (7) (8)	(1) the wound healing time (2) the frequency of dressing change (3) hospitalization	Ⅲ	1 month	1 ~ 2 weeks.	50.6±10.3	45.9±12.2	NR	NR	every day or every other day	50/20

								costs									
Xiao-Rong Liu, 2012	October 2010 to March 2012	China	15	15	VAC	SWC	NR	(1) the wound healing time (2) complete ulcer healing rate (3) the frequency of dressing change	Ⅲ/Ⅳ	to cure	to cure	63．51±24．47		to cure	every 1~3d once	every day or every other day	66.7/40
Yan-Zhan	NR	China	26	20	NPWT	SWC	NR	(1) the wound healing time (2) the frequency	Ⅲ	to cure	to cure	65~82	63~85	to cure	5 d	1—2time／d	NR

								of dressing change (3) hospitalization costs								
Guang-Ting Zhou, 2014	February 2011 to February 2014	China	26	26	VSD	SWC	NR	(1) the wound healing time (2) workload (3) hospitalization costs	Ⅲ/Ⅳ	to cure	to cure	68．12±1．51	to cure	NR	NR	NR

Table.1 Characteristics of the included studies for meta-analysis of NPWT for III/IV PIs

VAC: Vacuum-Assisted Closure device; HP: the healthpoint system; (1)the sacrum; (2)occipital; (3)ankle; (4)femoral tuberosity; (5)ischial tuberosity; (6)heel;

(7)knee protuberant; (8)iliac crest

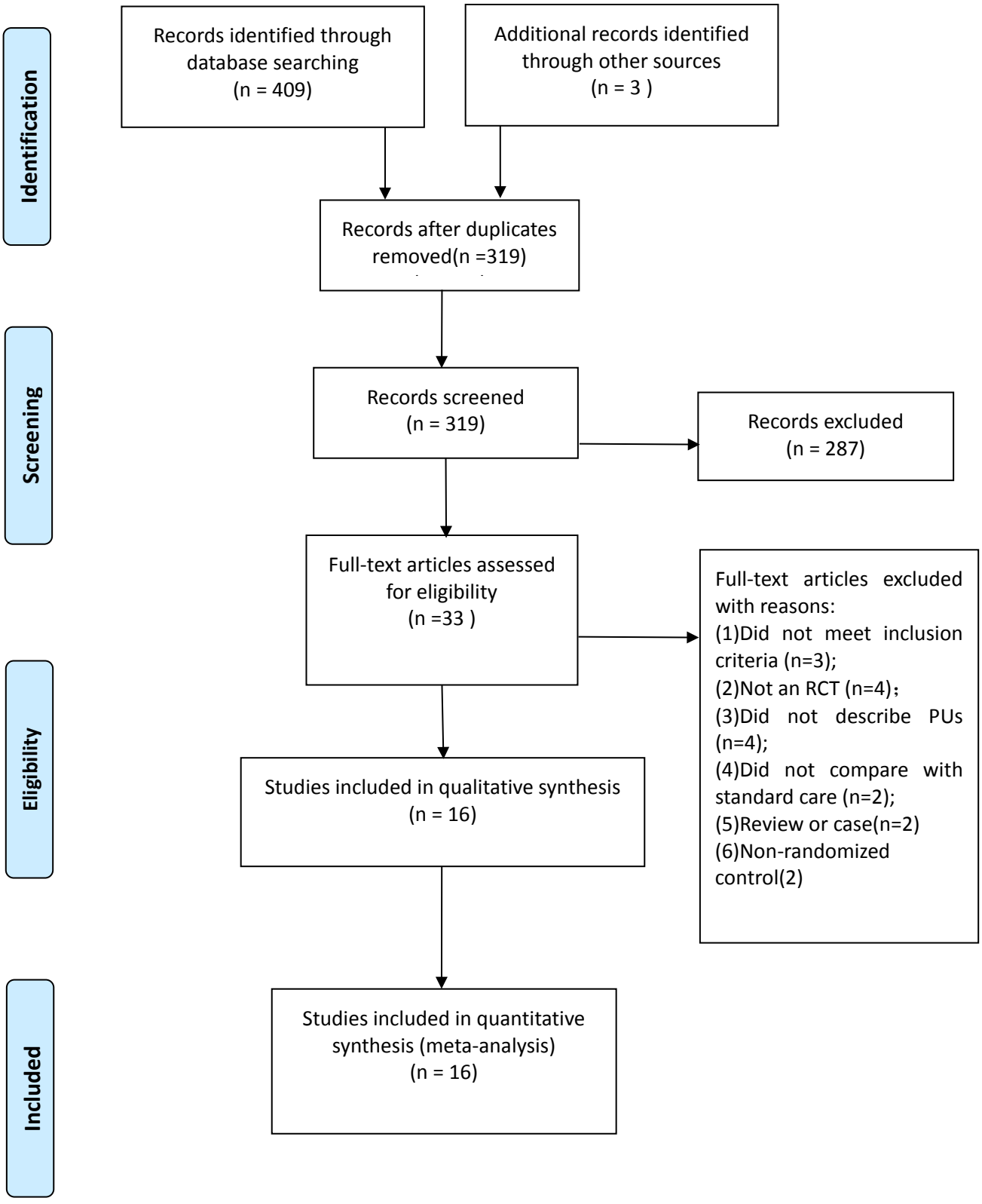
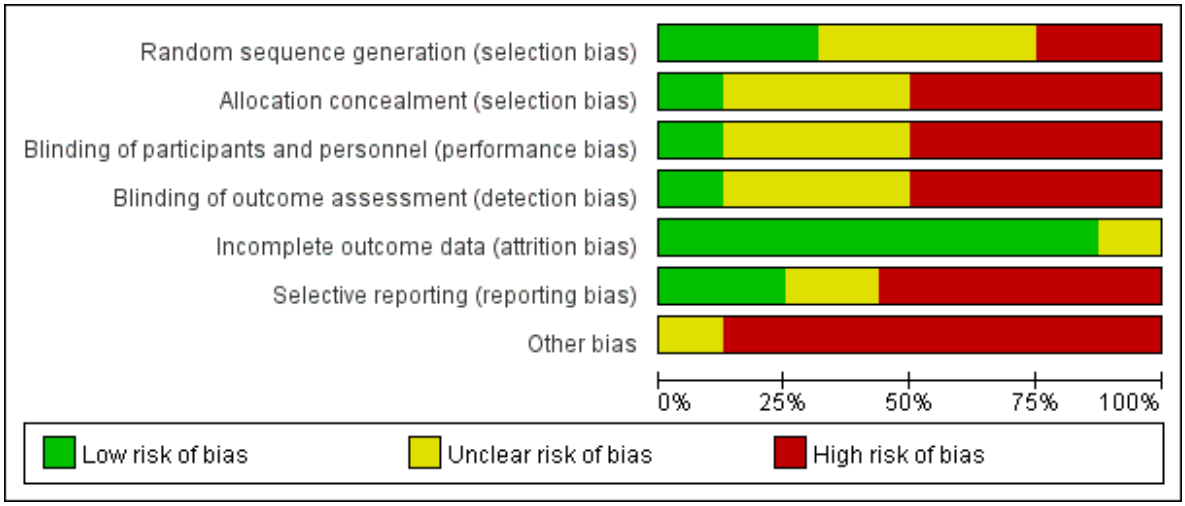


Fig.1 Article selection. The search strategy yielded a total of 16 articles for the meta-analysis. RCTs, randomized clinical trials.



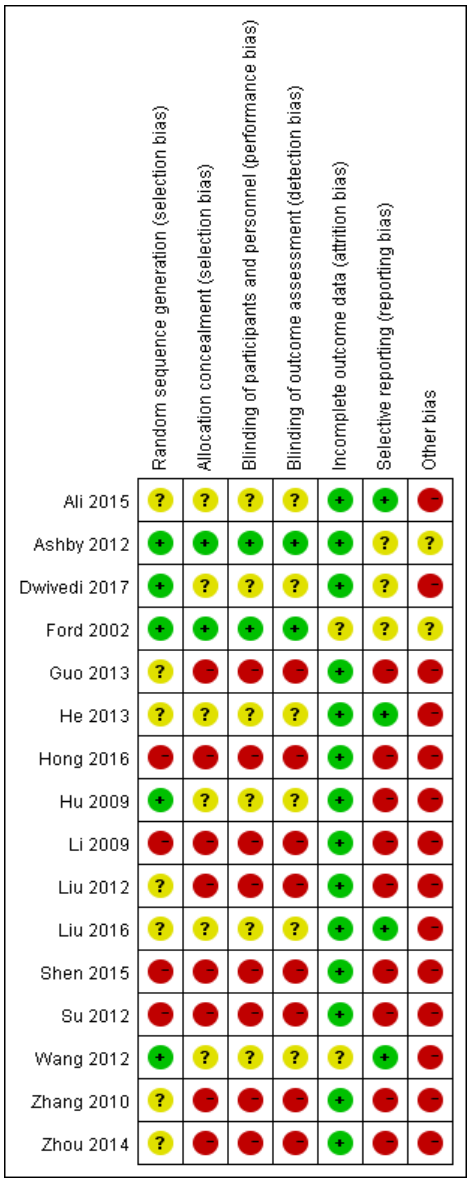
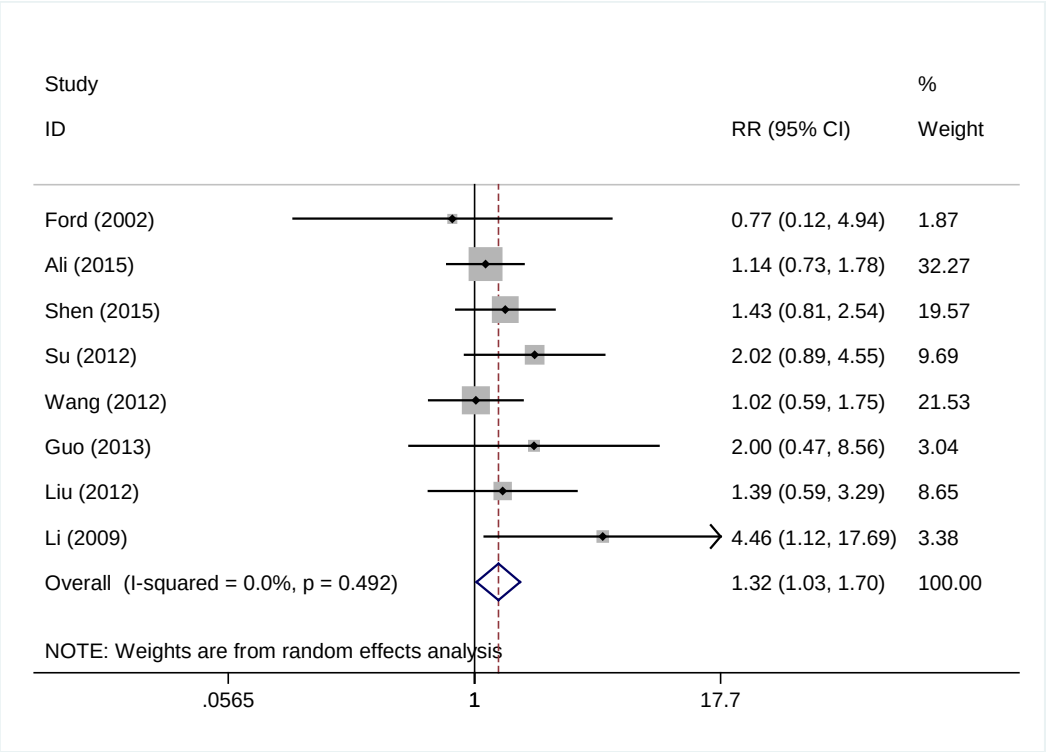


Fig.2 Risk of bias graph and summary.

Note: Review authors' judgments about each risk of bias item presented aspercentages across all included studies. Review authors' judgments about each risk of bias item for each included study.

a



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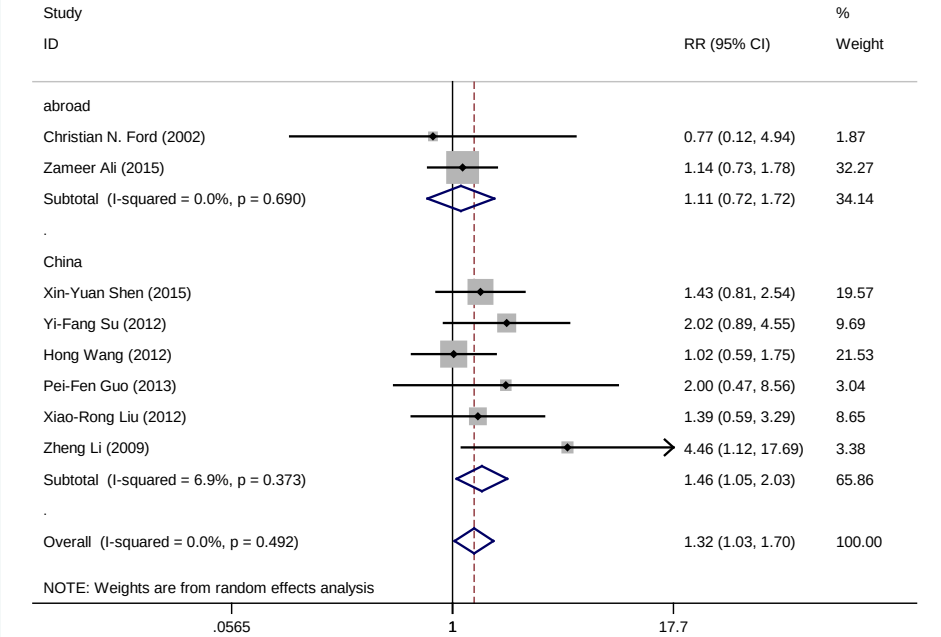

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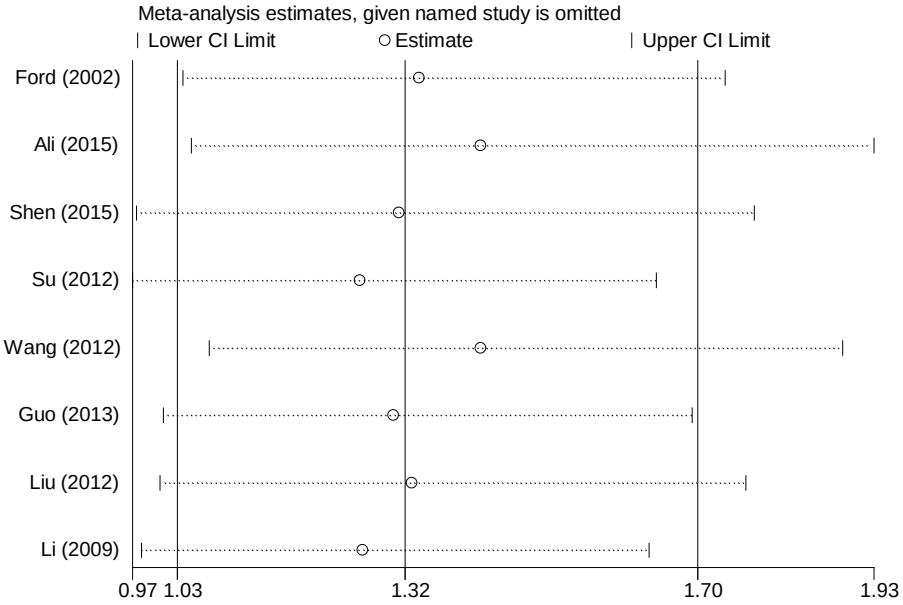
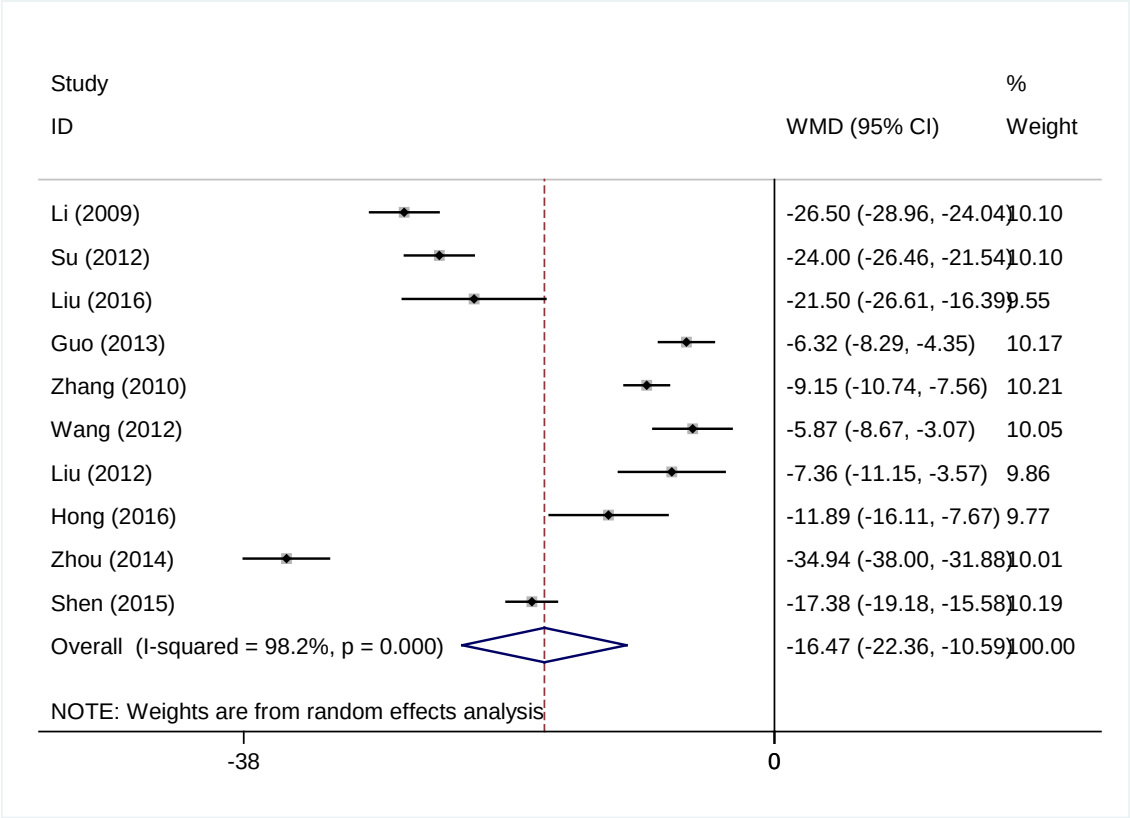


Fig.3 **a** Forest plot of the comparison of NPWT compared with SWC on the incidence of complete ulcer healing. Random effects model. RR=Random-effects model risk ratio; 95%CI=95% confidence interval. **b** Subgroups were selected based on the China and abroad country of wound healing rate. **c** Sensitivity analysis of the eight studies on the complete ulcer healing rate.

a



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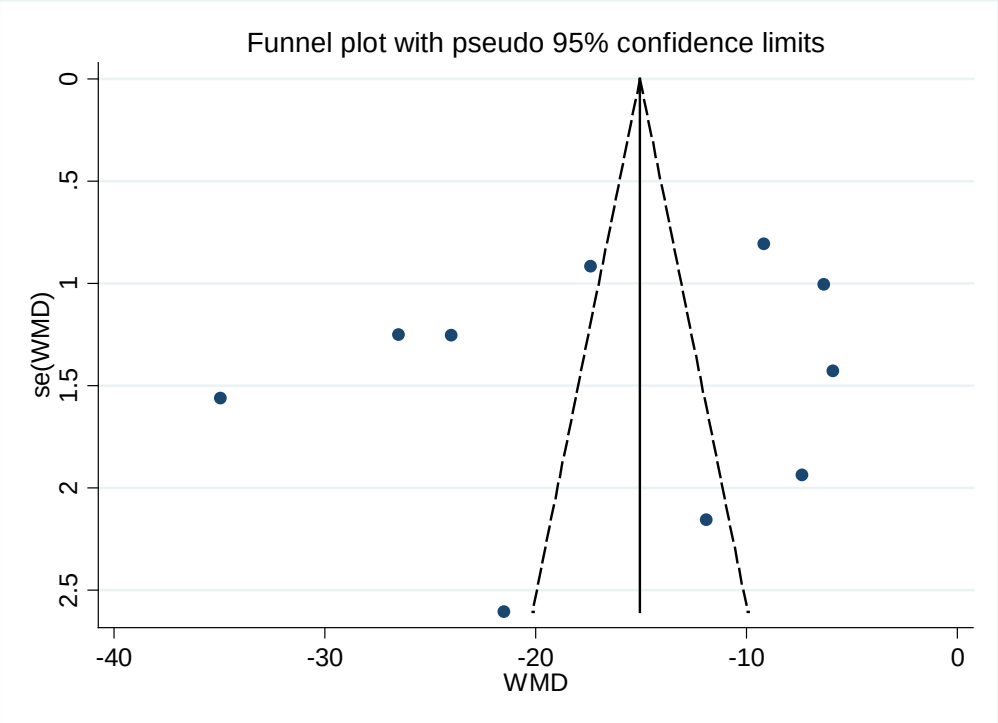

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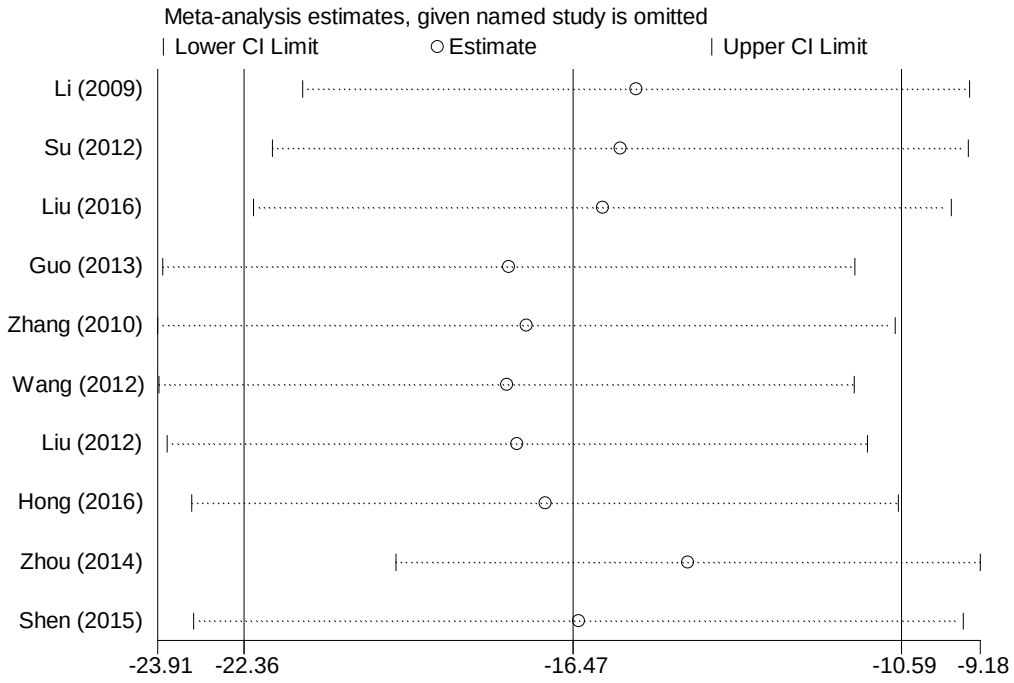

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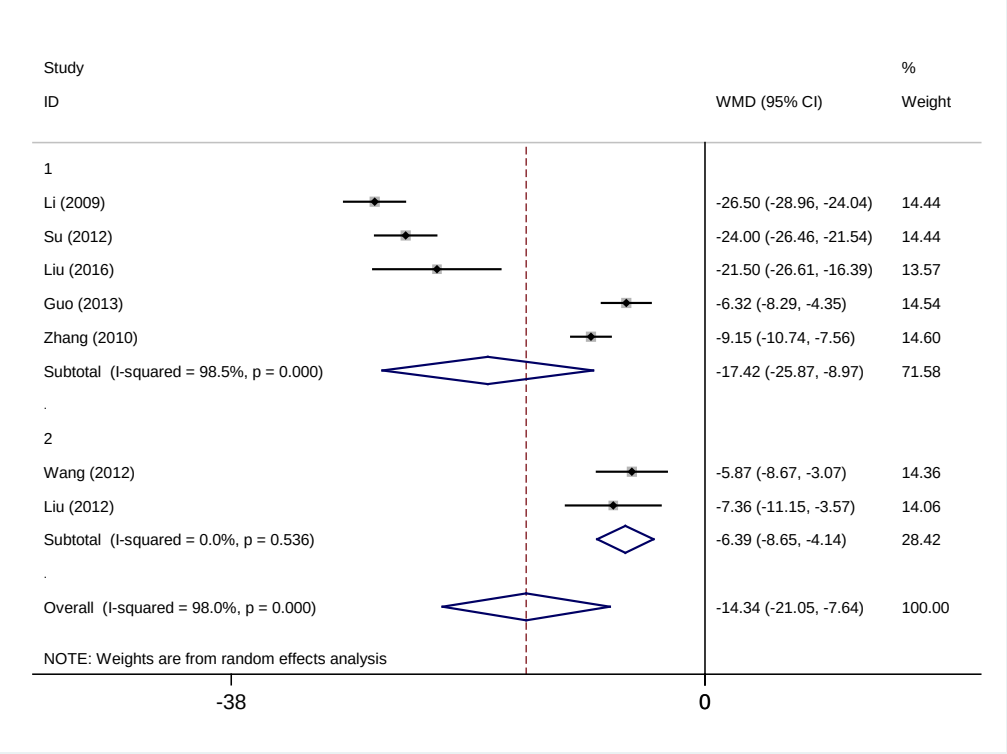


Fig.4 **a** Forest plot of the comparison of NPWT compared with SWC on the wound healing time. Random effects model. WMD=Wight Mean Difference. **b** Funnel plot of NPWT compared with SWC on Wound healing time. **c** Sensitivity analysis of the ten studies on wound healing time. **d** Subgroups were selected based on the definition of wound healing. 1: complete scab healing, 2: the growth of fresh granulation.

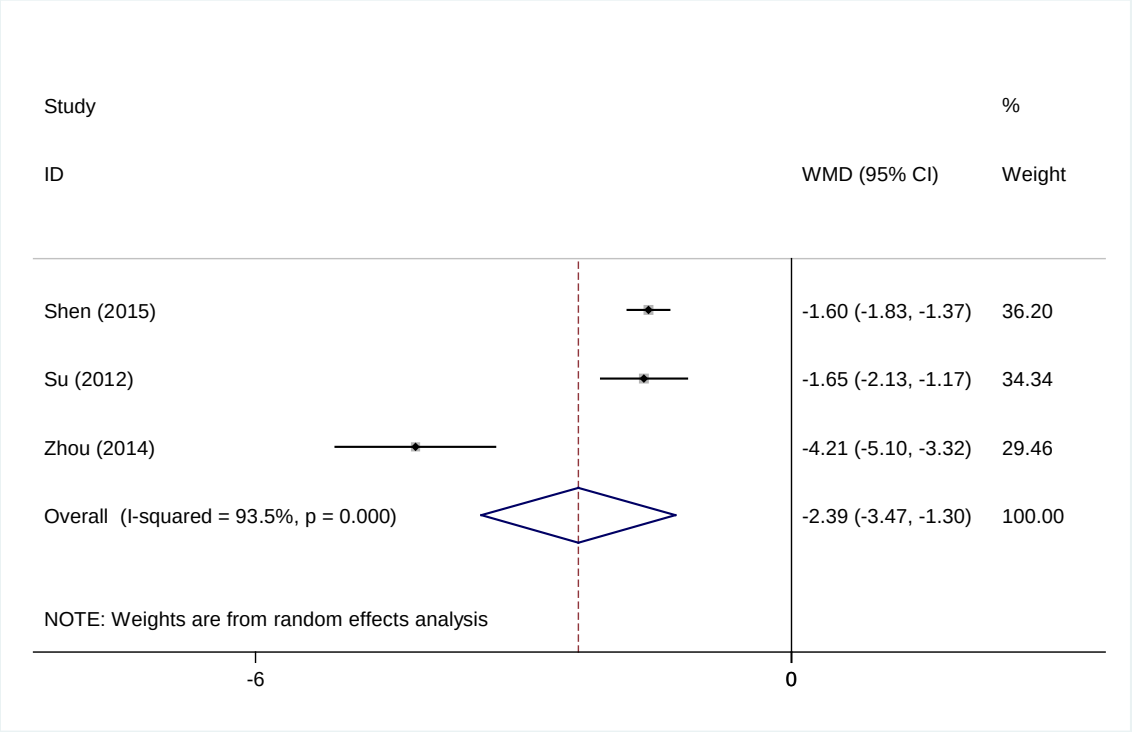
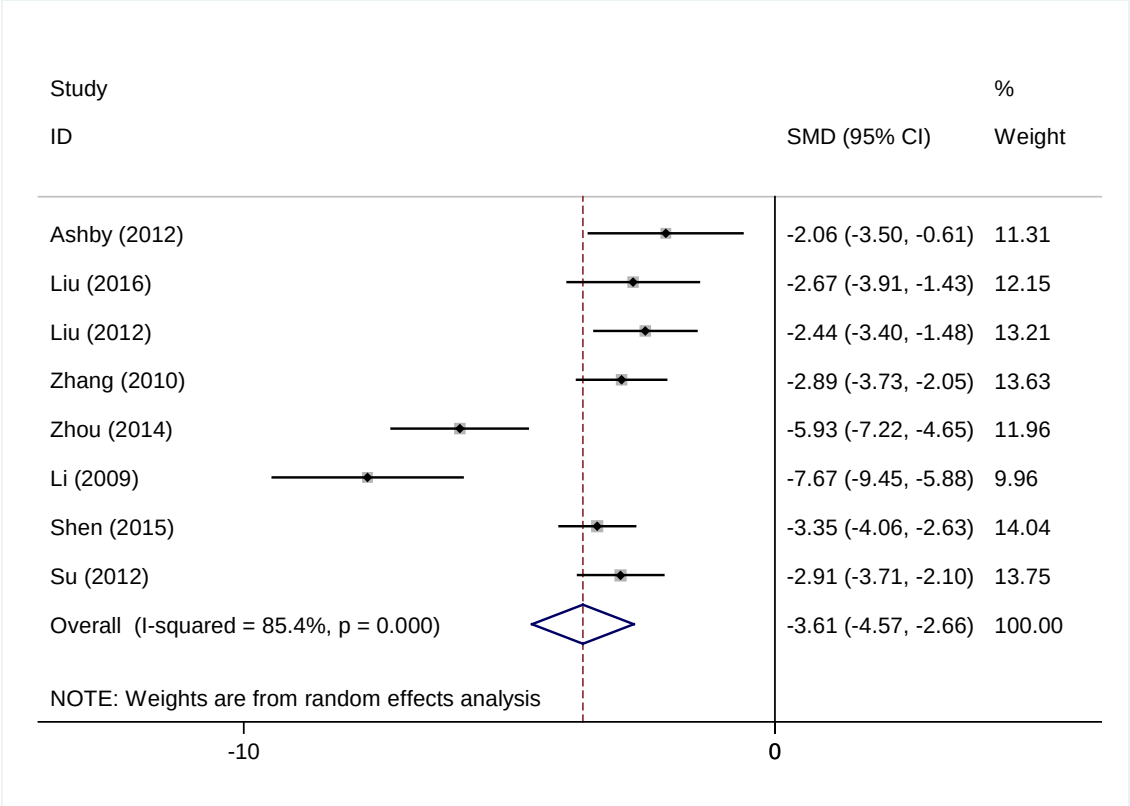
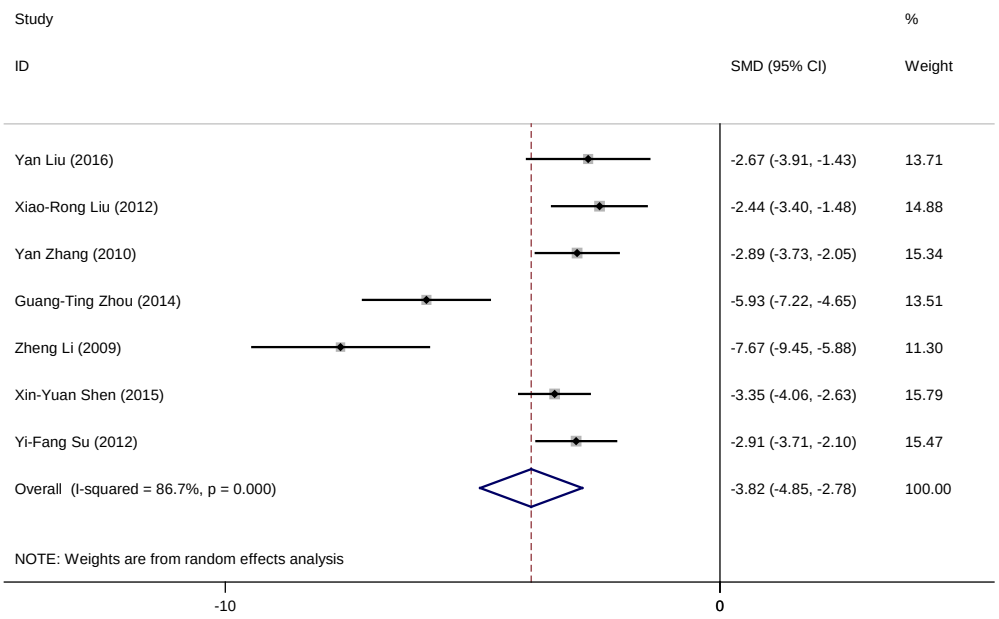


Fig.5 Forest plot of the comparison of NPWT compared with SWC on the pain score. Random effects model.

a



b



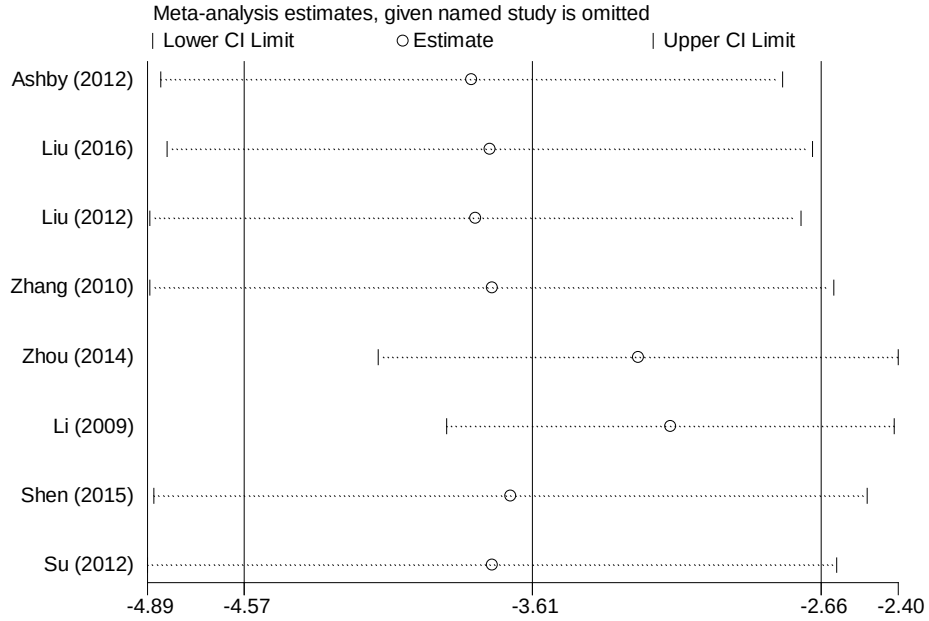
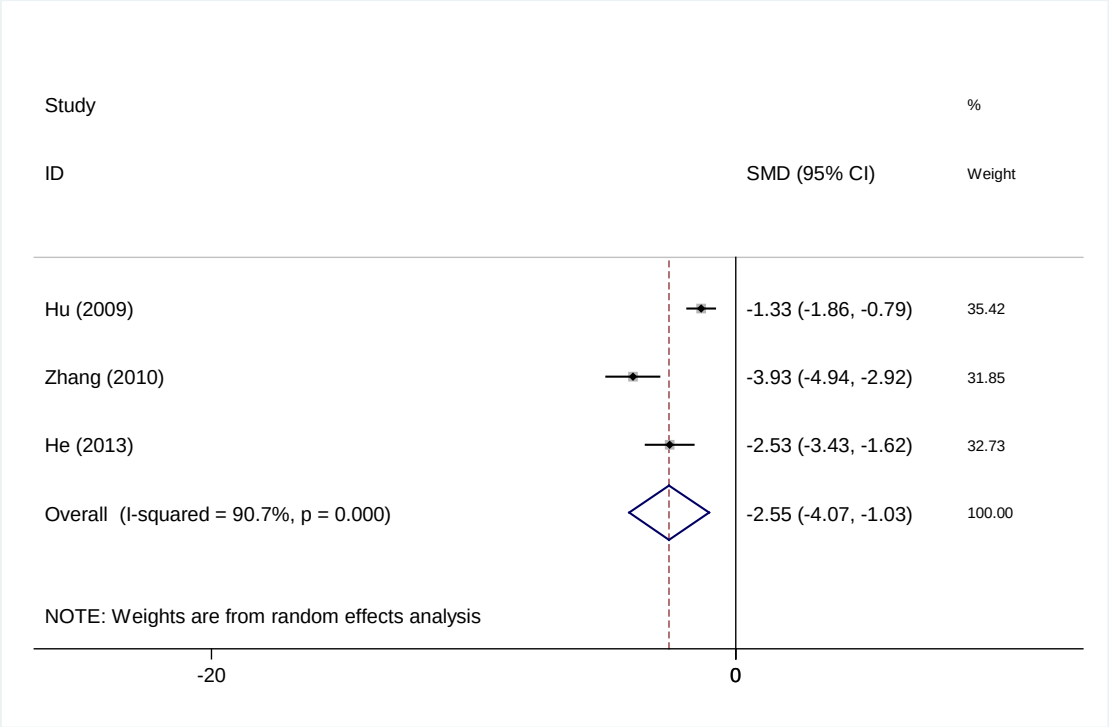


Fig.6 **a** Forest plot of the comparison of NPWT compared with SWC on the frequency of dressing change. Random effects model. SMD=STD Mean Difference. **b** Subgroups were selected based on the China and abroad country of the frequency of dressing change. **c** Sensitivity analysis of the eight studies on the frequency of dressing change.

a



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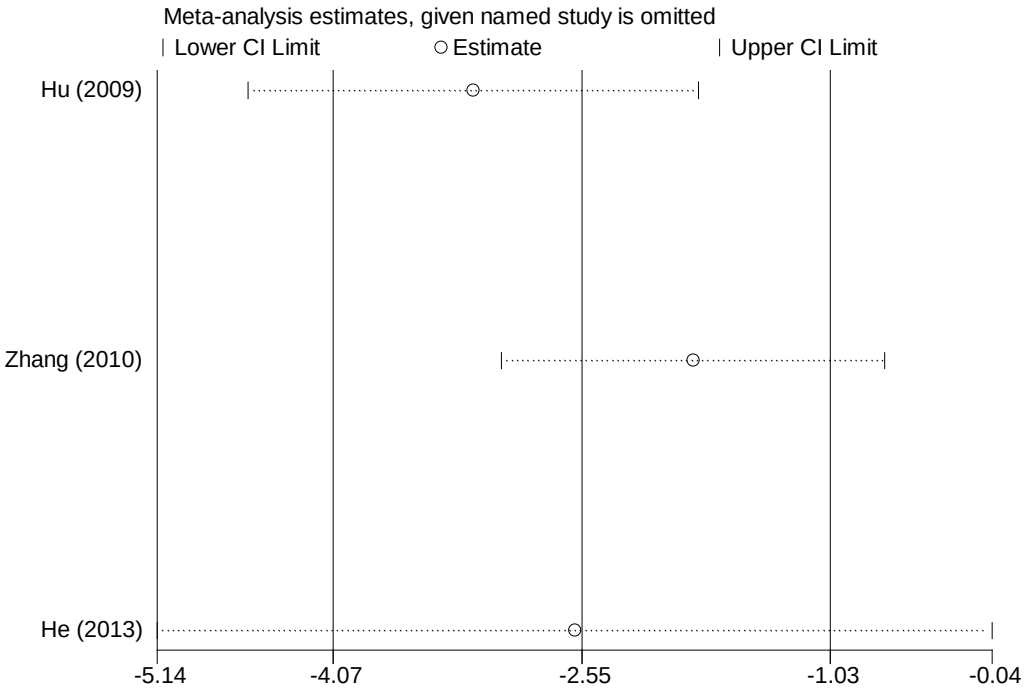

Fig.7 SMD=STD Mean Difference. **a** Forest plot of the comparison of NPWT compared with SWC on the hospitalization cost. Random effects model. **b** Sensitivity analysis of the three studies on the hospitalization cost.