Systematic Review and Meta-Analysis

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Naproxen for the treatment of neoplastic fever

A PRISMA-compliant systematic review and meta-analysis

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Abstract

Background: The effect of naproxen on the treatment of neoplastic fever is still unclear. A systematic review and meta-analysis were performed to investigate the effect of naproxen in the treatment of cancer fever or suspicion. Besides, the latest and most convincing evidence was provided for the earlier use of naproxen in treating cancer patients with fever of unknown origin.

Methods: A literature review was conducted to identify all published studies on the naproxen for the treatment of neoplastic fever. Electronic databases (eg, PUBMED, EMBASE and the Cochrane Library) were searched until October 2018. Data were extracted, and the risk of bias was assessed by 2 authors independently. Standard meta-analyses on the rate of successful treatment were conducted using a random-effects model, and relative risks were calculated with 95% confidence intervals (CIs).

Results: A total of 15 studies, recruiting 582 participants, were included, which were 1 randomized controlled trial (RCT), 1 non-RCT, 3 cross-sectional studies, and 10 case-series studies. The result of our meta-analysis revealed that the success rate on the treatment of neoplastic fever using naproxen was 94.1% (95% CI: 87.6%–97.3%). The success rate of the suspected neoplastic fever was 79.8%; for fever of unknown origin, it also reached 67.7%. In this meta-analysis, the success rate was 98.1% (95% CI: 95.0%–99.3%) in the dosage of 250 mg twice a day. Besides, a small dose of 125 mg naproxen, 375 mg twice a day and 250 mg 3 times a day were also useful. The result of the subgroup analysis revealed that the difference was not statistically significant in the treatment success rate for solid tumors and hematologic malignant.

Conclusions: The result of our meta-analysis suggested that naproxen exhibited a highly successful rate for the treatment of neoplastic fever. Besides, naproxen was also satisfactory in improving symptoms of suspected neoplastic fever and fever of unknown origin. The earlier use of naproxen might be able to mitigate cancer patient's suffering and enhanced their quality of life. These findings, however, rely primarily on observational data and should be interpreted rigorously. Further well-conducted trials are required to assess naproxen for the treatment of neoplastic fever.

Abbreviations: AHRQ = Agency for Healthcare Research and Quality, CI = confidence interval, IL = interleukin, NOS = Newcastle-Ottawa Scale, NSAIDs = nonsteroidal anti-inflammatory drugs, TNF = tumor necrosis factor.

Keywords: meta-analysis, naproxen, neoplastic fever, systematic review

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1. Introduction

Neoplastic fever, a fever caused by the cancer itself, has been reported as the most common cause of fever of unknown origin in cancer patients.[1] In general, neoplastic fever exhibits no clinical features to be differentiated from other types of fever because of infectious, rheumatic-inflammatory, or miscellaneous disorders.[2] Thus, neoplastic fever is a diagnosis of exclusion, that is, it can be established only after exhaustive evaluation and exclusion identifiable etiologies in the patient with cancer.[3] The generally recognized diagnostic criteria for neoplastic fever are presented as follows:[1]

- Temperature >37.8°C at least once a day;
- Duration of fever >2 weeks;
- Lack of evidence of infection (eg physical examination, laboratory examinations, and imaging studies);
- Absence of allergic mechanisms (eg, drug allergy, transfusion reaction, and radiation or chemotherapeutic drug reaction);
- Lack of response of fever to an empiric, adequate antibiotic therapy for at least 7 days;
- Prompt complete lysis by the naproxen test with sustained normal temperature while receiving naproxen.

Naproxen test was first proposed by Chang and Gross in 1984.[4] This study showed that the fever was completely abated within 24 hours in patients with neoplastic fever, and the afebrile

state was sustained as long as the patients were maintained on naproxen.[4] Naproxen test, a reliable method, was used to identify neoplastic fever from non-neoplastic fever in cancerous patients. The test result was positive when there was a rapid or sustained defervescence during the 3 days of the naproxen test. However, the temperatures of patients with infectious diseases were slightly or not dropped during the test period. Subsequently, a series of studies were conducted to verify the role of naproxen in the treatment of neoplastic fever patients.[5–9]

The additions of naproxen, ibuprofen, rofecoxib, diclofenac, indomethacin, and other non-steroidal anti-inflammatory drugs (NSAIDs) have also been demonstrated having the therapeutic effect on neoplastic fever.[10,11] Although the difference of the antipyretic activity in various NSAIDs is not statistically significant, the response to these drugs was faster in naproxen than that in the other NSAIDs. Furthermore, the experience of these drugs used in neoplastic fever is also limited.

Besides the NSAIDs, corticosteroids are also vital to abate fever caused by various etiologies (eg, infections, allergic reactions, collagen vascular diseases, and malignancy).[12] In one retrospective study, the antipyretic effects of corticosteroids and naproxen on neoplastic fever were compared.[13] The result suggested the naproxen treatment led to the complete lysis of neoplastic fever in 90% patients, and corticosteroids brought about lysis of fever in only 50% patients.[13] Thus, naproxen, compared with corticosteroids, was more effective for neoplastic fever.

The mechanisms, by which malignancies induce fever, are still unclear, and they seem to be distinct from the fever because of infection. At present, it is generally recognized that the release of pyrogenic cytokines, especially interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF) alpha, and interferon, either directly from tumor cells or from macrophages responding to tumor, can play a major role.[14] However, the exact pathophysiology of neoplastic fever and its difference from other causes of fever remain uncertain. Thus, specific mechanisms for cytokine-mediated neoplastic fever induction have not been established.[1]

Although the studies about naproxen for the treatment of neoplastic fever have reported a lot in the last few decades,[15,16] owing to small sample sizes, these evidences were not adequately powered to detect the effect of naproxen in fever patients with cancer. Besides, a thorough clinical examination, the appropriate laboratory and imaging studies, as well as an adequate empiric antibiotic treatment were recommended before the consideration of the use of the naproxen. These workups could lead to unnecessary and prolonged hospitalization of patients with advanced cancer and limited life expectancy, thereby causing their huge suffering. In this scenario, it might be more important to control symptoms effectively and avoid unnecessarily burdensome treatments as much as possible.

Therefore, we performed a systematic review and meta-analysis to explore the effect of naproxen in the treatment of neoplastic fever or suspicion. Furthermore, we provided the latest and most convincing evidence for the earlier use of naproxen in cancer patients with fever of unknown origin and decreased these patient's suffering and enhanced their quality of life.

2. Materials and methods

2.1. Selection criteria

The inclusion criteria in the study were as follows: population (fever in patients with cancer); intervention (naproxen); comparison (other NSAIDs, previous and subsequent intervention or nonintervention); outcome (rates of successful treatment); design (all types of clinical studies) (ie, randomized controlled trials [RCTs], non-RCTs, cohort studies, case–control studies, and case-series studies), involving naproxen for the treatment of neoplastic fever.

2.2. Search strategy

All studies reporting the naproxen for the treatment of neoplastic fever in the Cochrane Library, Embase, and PubMed were searched. Search terms included those related to neoplastic fever, naproxen, and their variants. The search strategies for PubMed and Embase are listed in Table 1. The data were searched from work of the database to October 2018. No language restriction was imposed, whereas only the studies conducted on human adult subjects were selected. Furthermore, to identify additional published articles, all references in eligible articles were extensively reviewed. In addition, the bibliographies of previous reviews and included trials to identify other potentially eligible trials were achieved manually by Wu and Lin.

2.3. Selection of studies and data extraction

In terms of the PRISMA guidelines, the initial screening was independently performed by 2 authors (Zhang and Huang); obviously irrelevant titles and duplicate records were excluded from the first search. The remaining abstracts and potentially relevant full-text articles were obtained. Full-text articles were obtained when information given in the title or abstracts either satisfied to the selection criteria or could not be ascertained owing to the limited information. Any differences were resolved through discussion, and a consensus was reached among all the authors.

Data were extracted from the included studies. Each full-text article was reviewed by 2 authors independently (Zhang and Huang) for eligibility, and the following data were extracted from the eligible studies, which included year of issue, surname of first author, country, types of study design, number of participant, participant characteristics, intervention, and outcome. All the data were inputted into a standardized Excel 2007 form; any discrepancy was addressed by discussion and consensus.

Table 1

Search strategy.

Source: PubMed; searched on: July 29, 2018

Search	Query	Items found
#9	Search #5 AND #8	36
#8	Search #6 OR #7	6366
#7	Search Naproxen[Title/Abstract]	5644
#6	Search "Naproxen"[Mesh]	3849
#5	Search #3 OR #4	5799
#4	Search (Neoplastic Fever[Title/Abstract]) OR Tumor Fever[Title/Abstract]	56
#3	Search #1 AND #2	5779
#2	Search "Fever"[Mesh]	40410
#1	Search "Neoplasms"[Mesh]	3065139

Source: Embase; searched on: July 29, 2018

No.	Query	Results
#9	#5 AND #8	158
#8	#6 OR #7	25468
#7	naproxen': ab, ti	7843
#6	'naproxen'/exp	24788
#5	#3 OR #4	55927
#4	neoplasms fever': ab, ti OR 'tumor fever': ab, ti	46
#3	#1 AND #2	55911
#2	'fever'/exp	207670
#1	'neoplasm'/exp	4402232

2.4. Risk of bias assessment in included studies

The methodological qualities of the studies were assessed by 2 reviewers independently (Liu and Zhong). The methodological quality of RCTs was assessed using the Cochrane Collaboration's Risk of Bias tool[17]; the quality of non-RCTs was assessed using MINORS (methodological index for non-randomized studies).[18] Newcastle-Ottawa Scale (NOS) was used for cohort studies and case control studies.[19] The NOS is a 9-star rating system designed for case–control and cohort studies, containing 3 domains and 8 items. A maximum of 2 stars can be allotted in the item of comparability.[20] The other items will get a single star if appropriate methods have been reported. The quality of cross-sectional studies was assessed using 11 checklists recommended by the Agency for Healthcare Research and Quality (AHRQ).[21] If the answer is YES, the item will score 1; if the answer is NO or UNLEAR, the item will score 0. The quality evaluation is as follows: high quality = 8–11; medium quality = 4–7; low quality = 0–3. Differences were resolved by consensus.

2.5. Statistical method

Meta-Analyst Beta 3.13 software (Tufts Medical Center, Boston, MA) was used for data analysis. The indicators of rates (eg, rate of successful treatment) were analyzed using meta-analysis with the random-effects mode. Cochran Q statistics and I^2 metric test were used to estimate the heterogeneity of the studies. A value >50% to indicate substantial heterogeneity and sought the potential sources of heterogeneity (eg, clinical heterogeneity and methodological heterogeneity).[22] If the results of the studies could not be combined using meta-analysis (owing to significant clinical heterogeneity and unconventional methods used in the analysis of studies), they would be presented separately.

Finally, publication bias in the studies was assessed using Begg funnel plot.

All analyses were based on previous published studies; thus, no ethical approval and patient consent are required.

3. Results

3.1. Study identification and selection

A total of 195 records were retrieved from the database and 3 additional records were identified from other sources. With the deletion of the repetition clause, 162 records were eligible. On the basis of inclusion and exclusion criteria, 133 articles were excluded after a brief reading of the title and summary of the articles. Then, the rest of the 29 full-text articles were assessed for eligibility. The records concerning review, redundant publications, no available data, and case reports were excluded. Finally, 15 studies were included in the meta-analysis, and the selection process is shown in Figure 1.

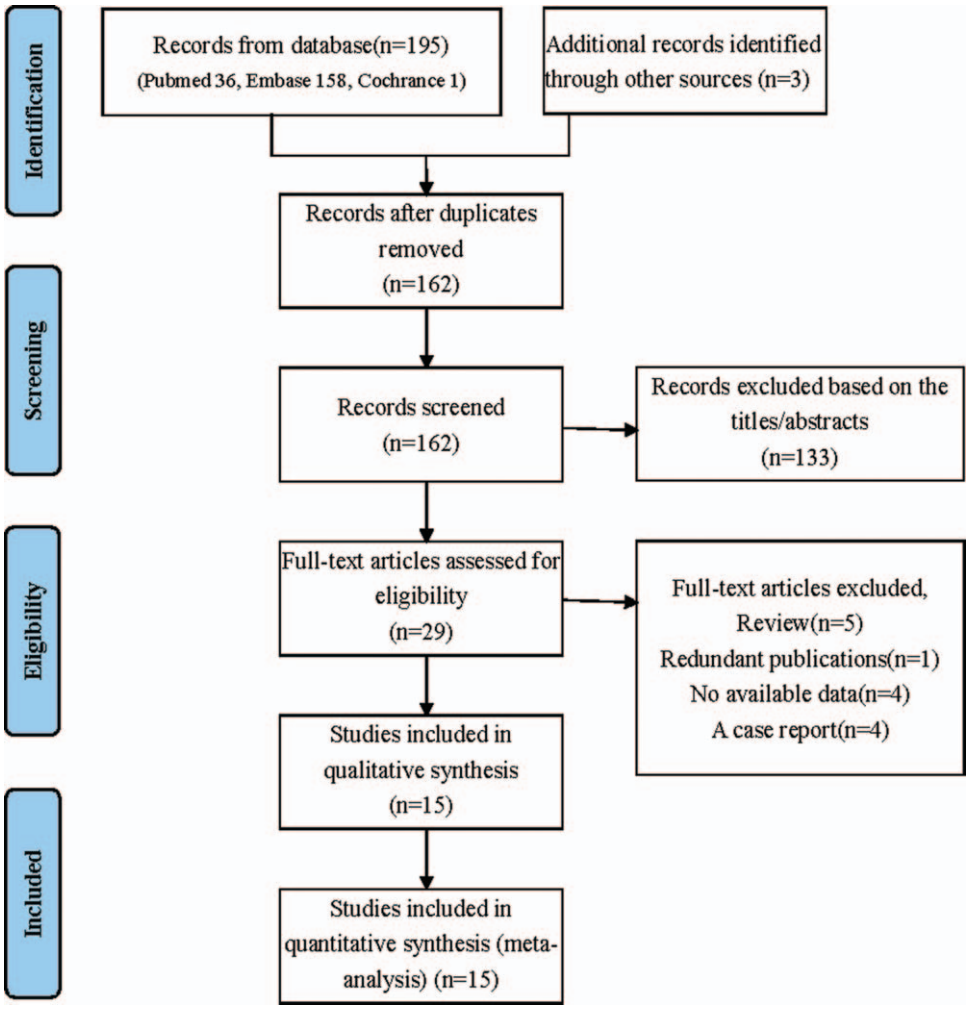

Figure 1. Selection process for the studies included in the meta-analysis.

Table 2

Characteristics of included studies.

Study	Country	Study design	Participants	Intervention	Outcome indicators
Chang and Gross 1984[4]	USA	Case-series study	22	Naproxen 250 mg Q12h for at least 3 days	Lysis of fever
Chang and Gross 1985[27]	USA	Case-series study	21	The initial naproxen dosage was 250 mg Q12h. Adequate treatment was 250 mg for at least 3 days. If partial or no response it was increased to 375 mg twice per day or up to 1500 mg/day.	Lysis of fever
Geisler et al, 1985[5]	Denmark	Cross-sectional study	28	Naproxen 125 mg	Lysis of fever
Chang, 1987[28]	USA	Case-series study	62	Naproxen 250 mg was given every 12 h for 36 h. If no response, the dosage was increased to 375 mg for 72 h.	Lysis of fever
Azeemuddin et al, 1987[6]	USA	Case-series study	16	The naproxen dosage was 7.5 mg/kg/dose at 12-hour intervals. Naproxen was continued for 7 days.	Lysis of fever
Kondo et al, 1987[7]	Japan	Case-series study	21	The naproxen doses ranged from 300 to 600 mg/day	Lysis of fever
Chang, 1988[13]	USA	Cross-sectional study	39	Naproxen at a dosage of 250 mg Q12h. If defervescence was prompt and complete, naproxen was continued for >3 days. If lysis of fever was absent or partial, the dosage was increased to 375 mg Q12h.	Lysis of fever
Tsavaris et al, 1990[11]	Greece	Randomized controlled trial	48	Naproxen 250 mg Q12h; diclophenac sodium 25 mg, 3 times daily; Indomethacin 25 mg, 3 times daily P.O. for 10 days	Lysis of fever; the speed of the response to the drugs
Tsavaris et al, 1991[8]	Greece	Controlled Clinical Trail	56	Naproxen 250 mg. twice a day at 12 h for 10 days.	Lysis of fever; the speed of the response to the drugs
Tsavaris et al, 1995[24]	Greece	Case-series study	82	Oral naproxen 250 mg Q12h. Fever was monitored for 10 days after initiation of treatment with naproxen.	Lysis of fever
Economos et al, 1995[23]	Chile	Case-series study	12	The dosage of naproxen was 250 mg orally Q8h. If a reponse was noted wihtin 24 h, naproxen was continued for 5 to 7 days.	lysis of fever
Liaw et al, 1998[25]	Taiwan	Case-series study	67	The dosage of naproxen ranged from 125 mg Q12h to 250 mg Q8h. The dosage of indomethacin ranged from 25 mg Q12h to 25 mg Q6h.	Lysis of fever
Vanderschueren et al, 2003[29]	Belgium	Cross-sectional study	77	250 mg twice daily (n 9 patients), 500 mg twice daily (n 45), or 500 mg thrice daily	Lysis of fever
Coşkun et al, 2012[9]	Turkey	Case-series study	20	Naproxen sodium, 500 mg every 12 h for 2 days.	Lysis of fever
Nakamura et al, 2016[26]	Japan	Case-series study	11	Naproxen was orally administered at a dose of 300–600 mg/day	Lysis of fever

3.2. Study characteristics

The main features of the studies listed are listed in Table 2.[4–9,11,13,23–29] The studies were published from 1984 to 2016. Of the 15 studies, 5 were from the United Stated, 6 were conducted in Europe (including 3 in Greece, and the other 3 in Denmark, Belgium, and Turkey, respectively). Among the rest studies, 2 were from Japan, 1 from Taiwan, and 1 from Chile. A total of 582 participants were recruited in the studies, with the age from 11 to 82 years. Among the 15 included studies, 1 was the RCT, 1 was the non-RCT, 3 were the cross-sectional studies, and the others were case-series studies. Furthermore, the outcome data of each included study are listed in Table 3.[4–9,11,13,23–29]

Table 3

Outcome data of Included Studies.

					Different dosage in successful treatment					
Study	Fever of undetermined origin	Suspected neoplastic fever	Neoplastic Fever	Successful treatment	125 mg	250 mg Q12h	375 mg Q12h	250 mg Q8h	250 mg Q6h	500 mg Q12h
Chang and Gross, 1984[4]	22	20	15	14		14				
Chang and Gross, 1985[27]		21	21	20		16	2	1	1	
Geisler et al, 1985[5]	28	13	13	13	13					
Chang, 1987[28]	68	64	50	48		48				
Azeemuddin et al, 1987[6]	16	16	14	14	7.5mg/kg Q12					
Kondo et al, 1987[7]	21	21	20	16	300–600 mg per day					
Chang, 1988[13]		39	39	39		37	2			
Tsavaris et al, 1990[11]		16	16	16		16				
Tsavaris et al, 1991[8]		56	56	56		56				
Tsavaris et al 1995[24]		82	64	64		64				
Economos et al, 1995[23]		12	10	10				10		
Liaw et al, 1998[25]		67	49	49	13	12	12	12		
Vanderschueren et al, 2003[29]	77	11	11	6		6				
Coşkun et al, 2012[9]		1	1	1						1
Nakamura et al, 2016[26]		11	9	8			300–600 mg/day			

Table 4

NICE Quality assessment for case series.

Study	Items	1	2	3	4	5	6	7	8	Score
Chang and Gross, 1984[4]		No	Yes	Yes	Yes	No	No	Yes	Yes	5
Chang and Gross, 1985[27]		No	Yes	Yes	Yes	No	No	Yes	Yes	5
Chang, 1987[28]		No	Yes	Yes	Yes	No	No	Yes	Yes	5
Azeemuddin et al, 1987[6]		No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	7
Kondo et al, 1987[7]		No	Yes	Yes	Yes	Yes	No	Yes	Yes	6
Tsavaris et al, 1995[24]		No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	7
Economos et al, 1995[23]		No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	7
Liaw et al, 1998[25]		No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	7
Coşkun et al, 2012[9]		No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	7
Nakamura et al, 2016[26]		No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	7

Yes = 1.
No = 0.

3.3. Risk of bias assessment

The outcomes of bias risk assessment in the included studies are listed in Tables 3 and 4. [4,6,7,9,23–28] Based on the NICE Quality Assessment for Case Series, 6 studies[6,9,23–26] were rated as a total score of 7, 1 study[7] scored 6 and the other 3 studies[4,27,28] scored 5. All of these case series studies are low risk of bias. According to the AHRQ items to assess the risk of bias of the cross-sectional studies, 2 studies[5,29] scored 7 and 1[13] scored 6, which are classified as the moderate quality (Table 5).[5,13,29]

In the study of included RCT,[11] the risk of bias was determined as "low" because of an inadequate randomization procedure. Besides, the blinding method and allocation sequence concealment were not reported in this study. In the non-RCT study,[8] MINORS global scores were 14 by summing all 12 item scores, indicating a low quality.

3.4. Treatment success rate

In this systematic review, 15 studies, involving 388 cases, provided data on naproxen for the treatment of neoplastic fever. In these studies, the successful rate of treatment varied from 54.5% to 100%. Moderate heterogeneity ($I^2 = 35\%$, $P = .007$) appeared among studies, and the random-effects model was employed. The pooled success rate reached 94.1% (95% CI: 87.6%–97.3%; Fig. 2).

For suspected neoplastic fever, 15 studies involving 450 subjects received naproxen for the treatment. Moderate heterogeneity ($I^2 = 29\%$, $P = .041$) appeared among studies. The pooled estimated success rate by the random-effects model was 79.8% (95% CI 72.5%–85.5%; Fig. 3).

For fever of unknown origin, naproxen was administered for 227 cases in 6 studies. In these studies, treatment success rate ranged from 43.1% to 87.5%. Moderate heterogeneity ($I^2 = 42\%$, $P = .001$) appeared among studies, and the random-effects model was employed. The pooled estimated success rate reached 67.7% (95% CI 54.3%–78.8%; Fig. 4).

Hematologic malignant and solid tumors are 2 different types of neoplasm. Accordingly, it is necessary to conduct subgroup analyses for different types of neoplasm. For solid tumors, 12 studies recruited 311 participants, and pooled estimated success rate using the random-effects model was 79.2% (95% CI: 71.2%–85.4%; Fig. 5). For hematologic malignant, 9 studies with a total of 94 cases were involved. Based on our analysis, the pooled estimate of success rate reached 82.0%, and the 95% CI was 67.1% to 91.0% (Fig. 6).

3.5. Therapeutic dose

Dosage is crucial for the treatment of any disease. It was reported that adequate dose of the drug was administered; patient with neoplastic fever responded to naproxen treatment in a prompt

Table 5

AHRQ quality assessment of included cross-sectional studies.

Study	Geisler et al, 1985[5]	Chang, 1988[13]	Vanderschueren et al, 2003[29]
Items			
1	Yes	Yes	Yes
2	Yes	Yes	Yes
3	Yes	Yes	Yes
4	Unclear	Unclear	Unclear
5	Unclear	Unclear	Unclear
6	Unclear	Unclear	Unclear
7	Yes	Yes	Yes
8	Yes	Unclear	Unclear
9	Yes	Yes	Yes
10	Yes	Yes	Yes
11	Unclear	Unclear	Yes
Quality scores	7	6	7

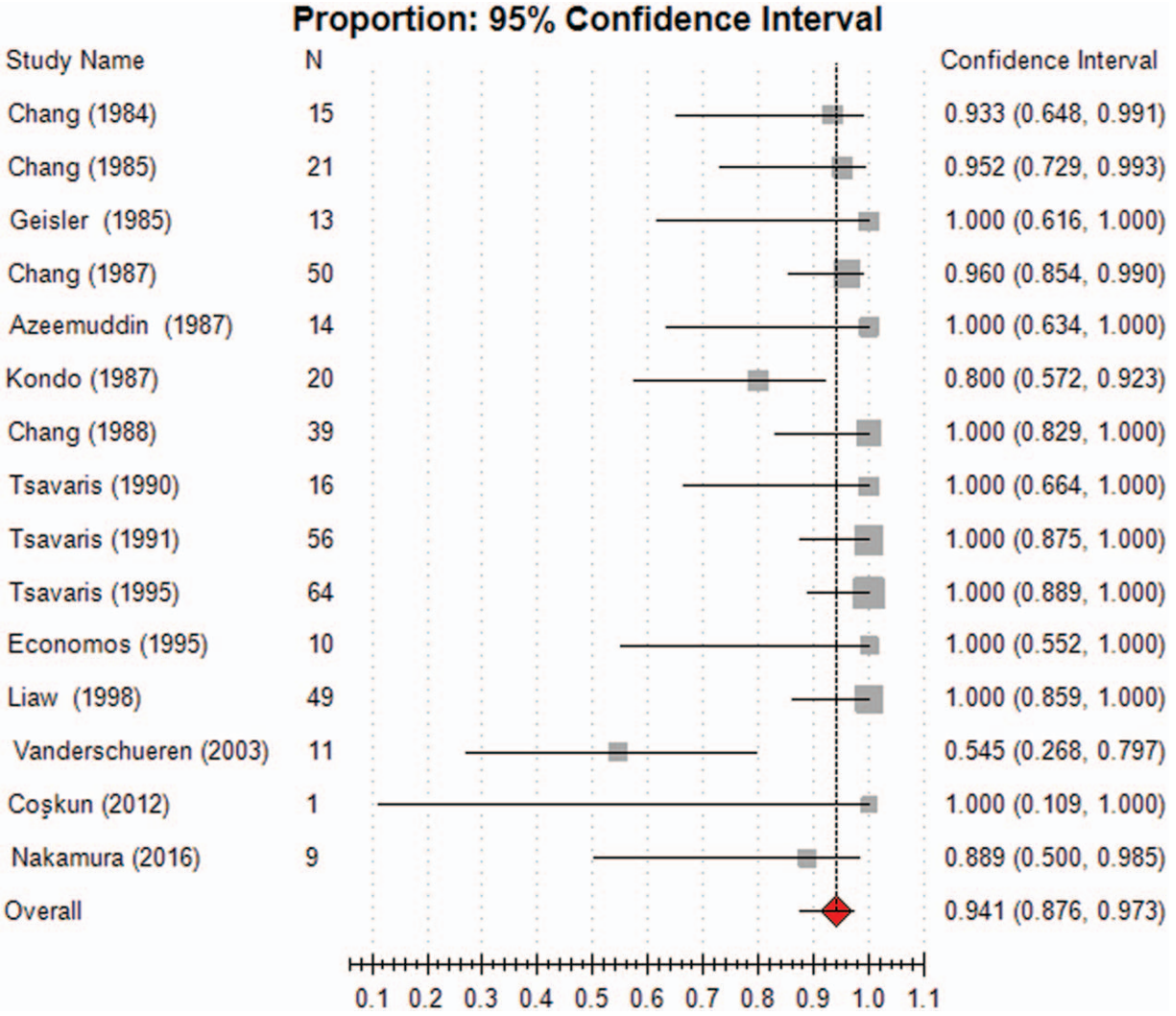

Figure 2. Forest plot of treatment success rate on naproxen for neoplastic fever.

and complete manner.[27] In general, the dose of 250 mg twice per day was the most common usage. Besides, 375 mg twice a day and 250 mg 3 times a day were also used in the patient with no response to the dosage of 250 mg twice a day. In this systematic review, 8 studies involving 257 patients adopted the dosage of 250 mg twice. Low heterogeneity ($I^2=0$, $P=.486$) appeared among studies, and the fixed-effects model was employed. The total effective rate was 98.1% (95% CI 95.0%–99.3%; Fig. 7) at the dose of 250 mg twice a day.

Besides, 2 studies[13,27] have reported the naproxen dosage was increased to 375 mg twice a day in 4 patients when lysis of fever was absent or partial in 250 mg twice a day. One study described 10 cases with 250 mg 3 times a day.[23] A higher dose appeared in only 1 neoplastic fever patient administrated with 500 mg twice a day.[9] All these higher doses of naproxen had complete response with lysis of fever. Furthermore, 125 mg naproxen was also mentioned in one study[5]; this small dose in 13 patients also had a significant effect.

3.6. Publication bias

For the meta-analysis of naproxen on treatment success rate for neoplastic fever, there was no significant publication bias by inspection of the shape of Begg funnel plot (Fig. 8).

4. Discussion

Our present meta-analysis revealed the success rate on the treatment of neoplastic fever using naproxen was 94.1% (95% CI: 87.6%–97.3%). For suspected neoplastic fever, success rate was 79.8%. For fever of unknown origin, it also reached 67.7%. Thus, naproxen should be the first choice for patients with neoplastic fever when other causes have been ruled out. In addition, the earlier use of naproxen was also critical to suspected neoplastic fever or fever with of unknown origin patients. Because of the earlier use of naproxen might mitigate cancer patient's suffering and enhanced their quality of life. However, during the use of naproxen, the common adverse reactions of NASID should be considered (eg, gastritis and gastrointestinal bleeding), as well as additional contraindications (eg, heart, kidney and liver dysfunction).[30]

Besides, it is noteworthy that fever persistence after naproxen treatment strongly suggests fever not because of neoplasm but because of an infection or other nonneoplastic

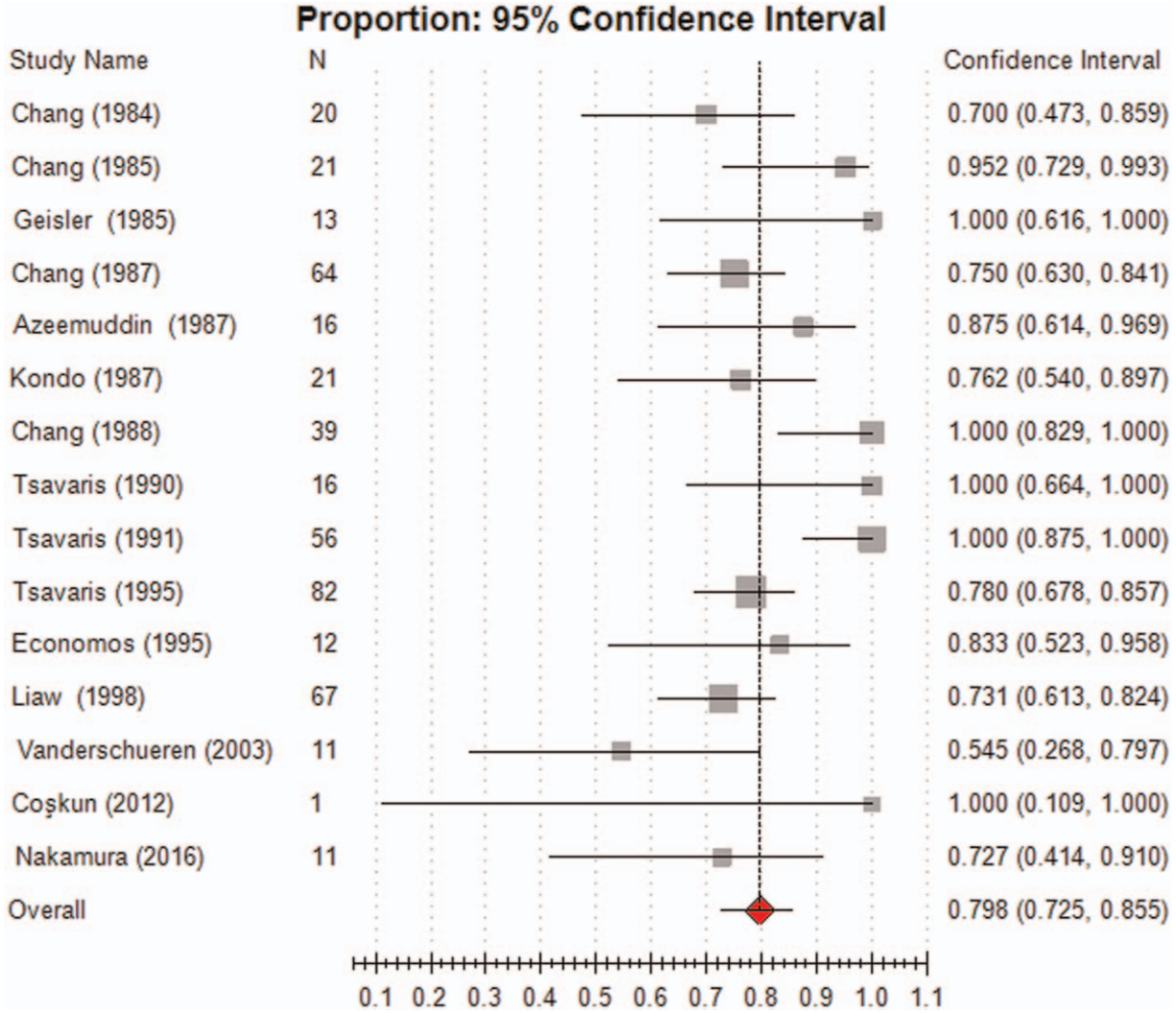

Figure 3. Forest plot of treatment success rate on naproxen for suspected neoplastic fever.

etiology and further evaluation must be continued. It was also reported that antibiotic treatments should be continued during the treatment of naproxen, which would not interfere with the results.[1]

The dosage of medication is important to the treatment of any condition. In this meta-analysis, a dose of 250 mg twice a day was not uncommon. The success rate of the treatment was 98.1% (95% CI 95.0%–99.3%). Moreover, small dose of 125 mg naproxen, 375 mg twice a day, and 250 mg 3 times a day were also useful in this systematic review. Thus, the recommended antipyretic dose range for naproxen was 125 to 750 mg/day, divided into 2 or 3 doses p.o. After 3-day treatment, plasma concentration of naproxen would be steady (5–6 half-lives). If fever continues with this dosage within 3 days, naproxen should be discontinued. In this circumstance, it should consider fever might not due to neoplasm, and further evaluation the factors of infection or other nonneoplastic etiology.

Solid tumors and hematologic malignancy (eg, Hodgkin lymphoma, non-Hodgkin lymphoma, and leukemias) are 2 types of malignancies. To determine whether neoplastic fever in these 2 types of malignancies reacts to naproxen in a similar effect, subgroup analyses were conducted. For solid tumors, pooled estimated success rate by the random-effects model was 79.2% (95% CI: 71.2%–85.4%), and the pooled estimate of success rate reached 82.0% (95% CI: 67.1%–91.0%) in hematologic malignant. There was no significant difference in treatment success rate. However, it was reported that paraneoplastic fever in hematologic malignant was more sensitive to naproxen administration during the first day.[8] The mean temperatures significantly dropped in hematologic malignant than that in solid tumors.

Although conducted comprehensively, several limitations should be considered when interpreting this result. First, this meta-analysis was not large sample size, and unpublished studies were not included. Besides, most of the included studies in our meta-analysis were observational studies. Selection bias and confounding could contribute to underestimates or overestimates of the actual effect of an intervention in these observational studies.[31] Moreover, other factors (eg, ethnicity and age) and environmental factors might have led to heterogeneity.

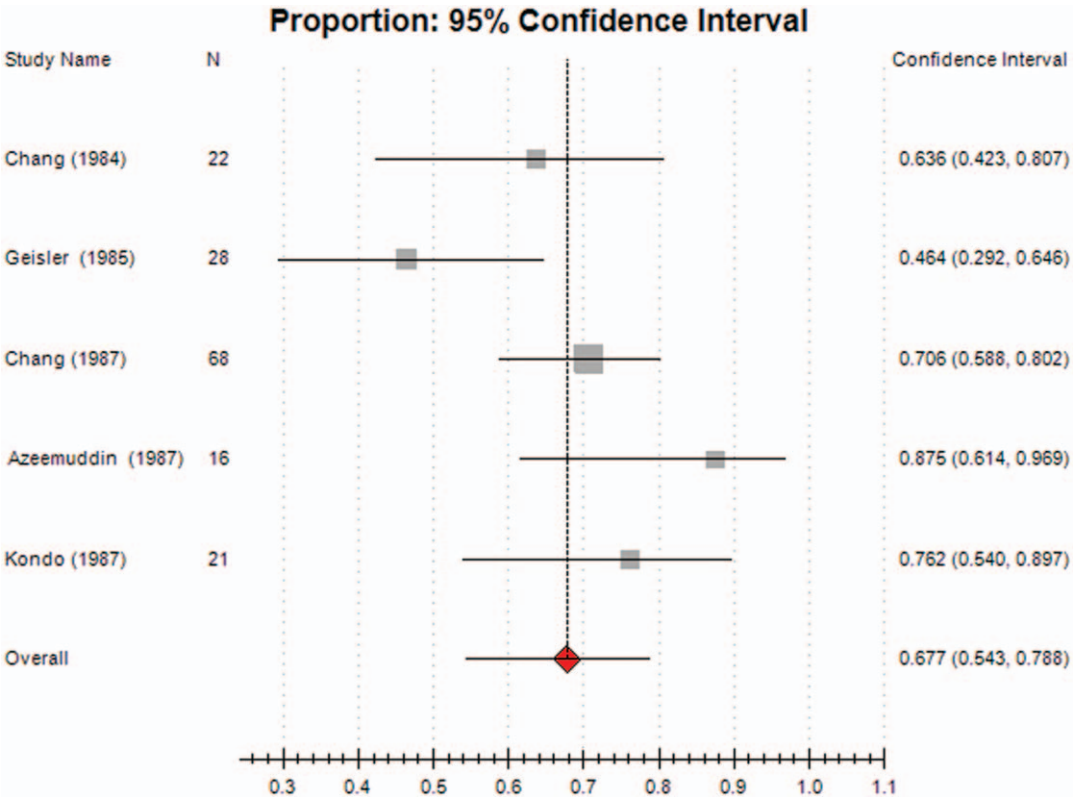

Figure 4. Forest plot of treatment success rate on naproxen for fever of undetermined origin.

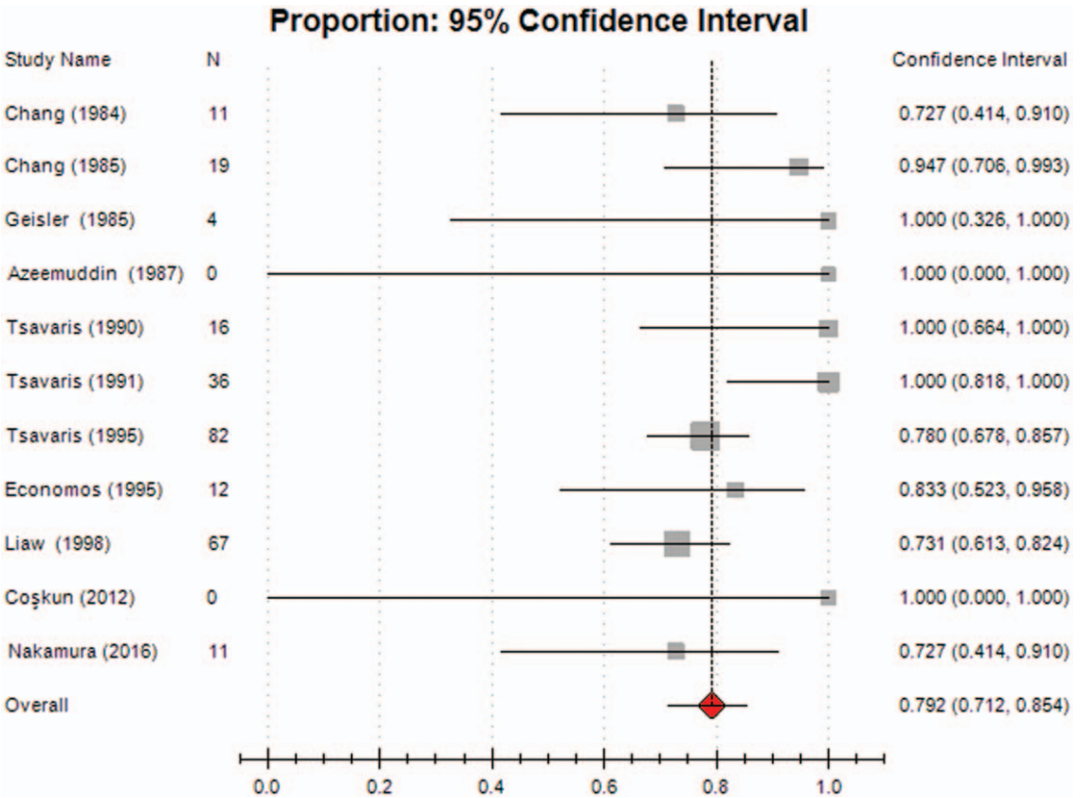

Figure 5. Forest plot of treatment success rate on naproxen for solid tumor.

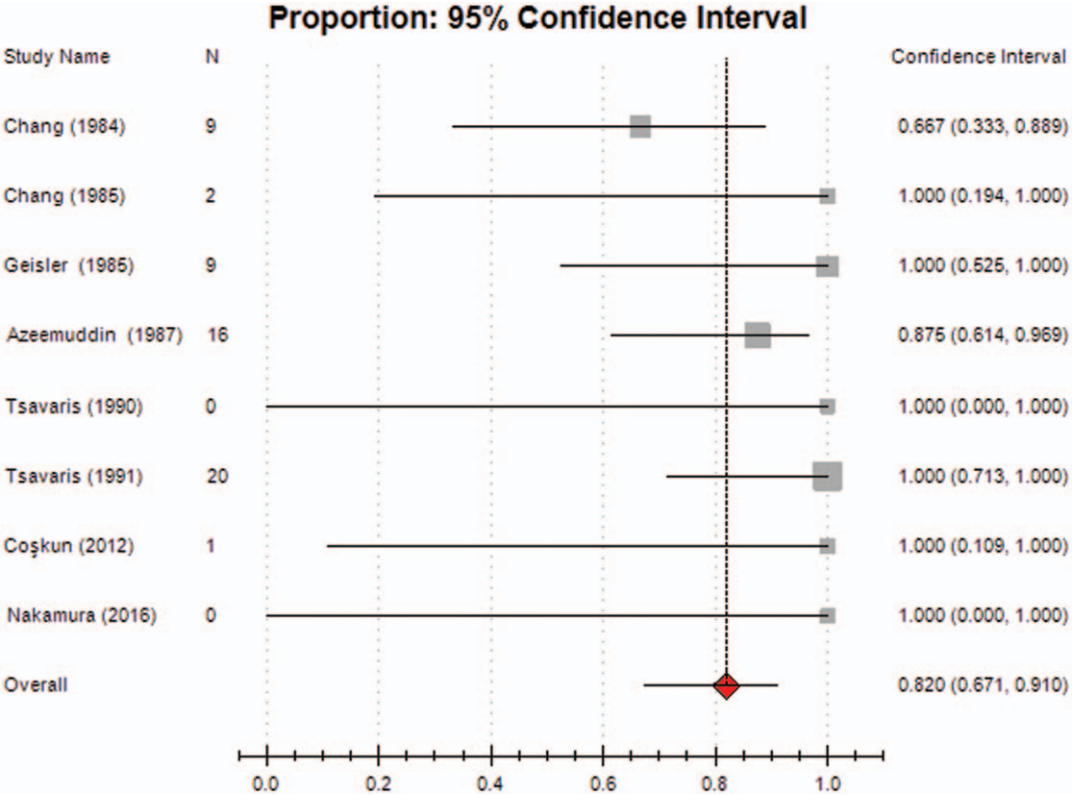

Figure 6. Forest plot of treatment success rate on naproxen for hematologic malignant.

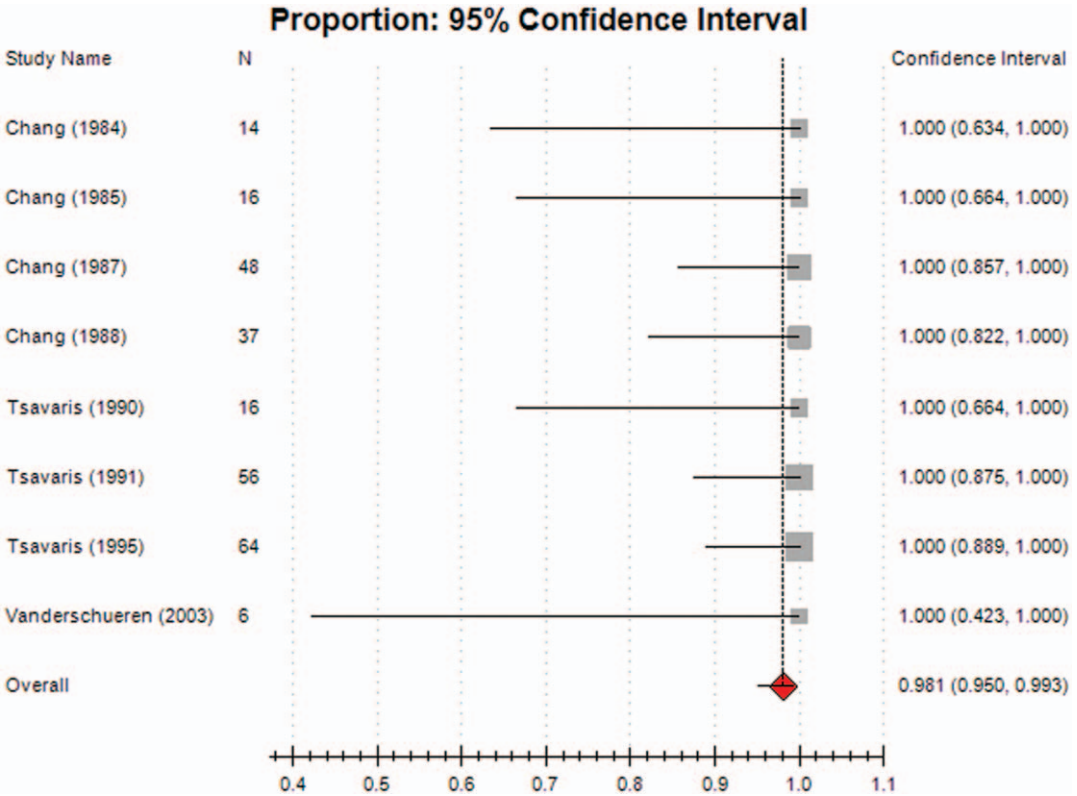

Figure 7. Forest plot of success rate in the dosage of 250 mg twice daily.

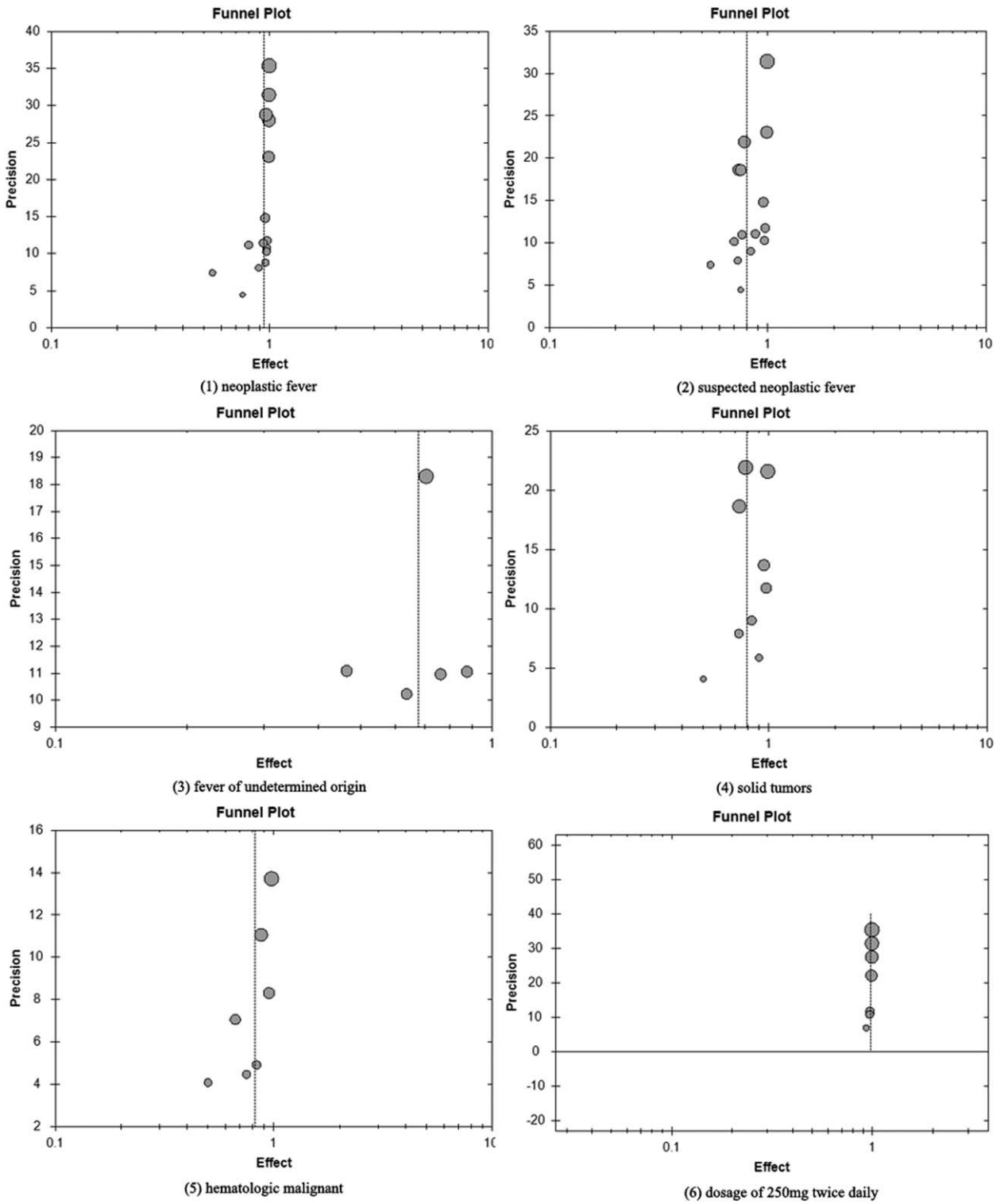

Figure 8. Funnel plot for assessing publication bias for neoplastic fever, suspected neoplastic fever, fever of undetermined origin, solid tumor, hematologic malignant, and dosage of 250 mg twice daily.

5. Conclusions

The present systematic review and meta-analysis suggested that naproxen had a highly successful rate for the treatment of neoplastic fever. Besides, naproxen was also satisfactory in improving symptoms of suspected neoplastic fever and fever of unknown origin. Thus far, neoplastic fever remains a diagnosis of exclusion. Once diagnosed, disease-specific palliative chemotherapy and surgery may be useful for controlling neoplastic fever. When that is not possible, the earlier use of naproxen should be a

good choice. Since the earlier use of naproxen might mitigate cancer patient's suffering and enhanced their quality of life. Another advantage of naproxen treatment is that it is inexpensive and affordable.

To the best of our knowledge, this systematic review is the first review systematically and quantitatively evaluating the roles of naproxen for the treatment of neoplastic fever. However, most of the included studies in this systematic review are small sample size and observational studies. Thus far, there are no well-designed studies to support its use. This may be influenced by selection bias, which should be carefully explained. Further high-quality and adequately powered RCTs are warranted.

Author contributions

Hongliang Zhang is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Yufang Yang and Xiaobin Zhong conceived and designed the study. Zhenguang Huang and Taotao Liu performed the statistical analysis. Zhongqiu Lin and Yuyong Wu carried out the literature search and data collection.
Data curation: Yuyong Wu.
Methodology: Zhongqiu Lin.
Project administration: Zhenguang Huang.
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