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Evaluation and Monitoring of Superoxide Dismutase (SOD) Activity and its Clinical Significance in Gastric Cancer: A Systematic Review and Meta-Analysis

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: This systematic review of the literature and meta-analysis aimed to review the evaluation and monitoring of superoxide dismutase (SOD) activity and its clinical significance in gastric cancer.

Material/Methods: Systematic review involved searching the PubMed, Embase, Ovid, and the China National Knowledge Infrastructure (CNKI) databases. Search terms included 'superoxide dismutase,' and 'gastric cancer.' Studies that included measurements of SOD activity in peripheral blood samples in patients with SOD activity compared with healthy controls. The study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Results: Ten controlled clinical studies were identified that included six studies that measured SOD in serum, three in erythrocytes, and one study that measured SOD on whole blood. Meta-analysis, using the standardized mean difference (SMD) and the 95% confidence interval (CI), showed that patients with gastric cancer had significantly decreased SOD activity when compared with the healthy controls (SMD, -0.840; 95% CI, -1.463 to -0.218; $p=0.008$). Subgroup analysis was conducted on SOD distribution in the blood (erythrocyte: SMD, -1.773; 95% CI, -2.504 to -1.042; $p=0.000$) (serum SMD, -0.322; 95% CI, -1.006-0.361; $p=0.355$) (whole blood: SMD, -1.251; 95% CI, -1.731 to -0.771; $p=0.000$) and for male subjects (SMD, -2.090; 95% CI, -2.725 to -1.456; $p<0.001$).

Conclusions: Meta-analysis showed that SOD measurements from blood samples, especially in erythrocytes, had potential as a diagnostic and monitoring parameter in patients with gastric cancer.

MeSH Keywords: **Blood • Meta-Analysis • Stomach Neoplasms • Superoxide Dismutase**

Full-text PDF: <https://www.medscimonit.com/abstract/index/idArt/913375>

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Background

In recent decades, there has been increasing evidence that reactive oxygen species (ROS), which includes superoxide and hydroxyl free radicals and hydrogen peroxide (H₂O₂), play an important part in the pathogenesis of malignancy. ROS cause DNA damage, resulting in gene mutation and abnormal cell proliferation and oncogenesis [1]. Also, chronic inflammatory stress associated with ROS is associated with an increased cancer risk through mechanisms other than genotoxicity [2]. Also, due to abnormal metabolism, cancer cells accumulate excess ROS, which can generate cell damage and induce apoptosis.

Under the pressure of cytotoxicity, cancer cells develop antioxidant systems [3]. Superoxide dismutases (SODs) are the main enzymes that form the first line of defense against oxygen-derived free radicals and catalyze the removal of superoxide free radicals [4], and under some circumstances, exposure to oxidative stress can lead to the rapid induction of enzyme synthesis. The regulatory functions of SODs in growth, metabolism, and the oxidative stress response are increasingly recognized as important for tumor progression and survival [5]. There have been studies that have shown SODs to be associated with gastrointestinal neoplasms [6], but a clear association remains to be determined.

Gastric cancer is an aggressive malignancy of the gastrointestinal tract that has a high mortality rate, with few non-invasive methods for diagnosis and monitoring gastric cancer. Tumor-associated antigens may be detected in the blood of patients with malignancy and although these may be potential diagnostic and prognostic biomarkers, currently, there is no protein serum biomarker that is specific for gastric cancer [7]. However, erythrocytes or serum obtained from human peripheral venous blood may provide a model for the study of the mechanisms of antioxidants, and have the relative advantage of availability and simple extraction.

There have been recent studies that have shown that SOD activity measured in the peripheral blood might be a promising new method for diagnosis and evaluating gastric cancer. Monari et al. [8] showed that the detection of SOD was associated with gastric cancer and proposed that this finding provided some insight into the molecular mechanisms of cancer development. Although the specific mechanisms involved in the progression of gastric cancer remain unclear, recent developments in molecular biology have resulted in an improved understanding of the molecular epidemiology, carcinogenesis, and pathogenesis of gastric neoplasms [8]. Molecular markers are now more commonly used in diagnosis, in the assessment of prognosis, and as targets for the treatment of malignant tumors [5].

Recent studies have focused on blood-based detection of SODs in patients with gastric cancer. However, inconsistent results have been reported. One study showed that serum levels of copper and zinc-containing SOD, which exists principally in the cytoplasm, has a role in cell protection against ROS [9], and was shown to be increased in patients with gastric cancer when compared with healthy subjects [10]. However, another study showed increased SOD activity in patients with gastric cancer when compared with healthy individuals [11].

Given the previously published findings, and the controversies that exist on the association between SOD and gastric cancer, a systematic review of the literature and meta-analysis aimed to review the evaluation and monitoring of SOD activity in patients with gastric cancer compared with healthy individuals.

Material and Methods

Conduct of the meta-analysis

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Supplementary Table 1) [12].

Search strategy

Two investigators performed an independent systematic search of the PubMed, Embase, China National Knowledge Infrastructure (CNKI), and Ovid databases. The last search was on August 6, 2018. The main search terms were 'superoxide dismutase' and 'gastric cancer'. The complete search terms for PubMed included 'gastric neoplasm', OR 'stomach cancer', OR 'gastric cancer', OR 'gastric carcinoma', OR 'stomach neoplasm', AND 'SOD', OR 'erythrocyte', OR 'hemocuprein', OR 'superoxide dismutase'. Figure 1 shows the search process used in this study.

Inclusion and exclusion criteria

Published studies were included that consisted of patients with a histologically confirmed diagnosis of gastric cancer as the study group, and healthy individuals as the control group. The activity of superoxide dismutase (SOD) in blood samples was the main measurement parameter used in the study and control groups. There were treatment interventions used, such as drugs or surgery in either group before the blood samples were obtained.

Publications were excluded from the meta-analysis if the data were incomplete or if they were conference abstracts, review articles, or animal studies.

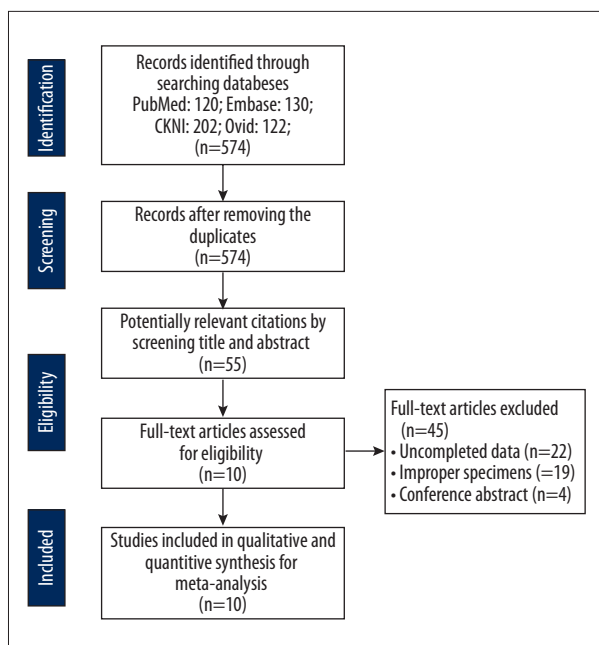


Figure 1. The literature search and publication selection process.

Data extraction

Two independent investigators extracted data from the eligible studies. The data included first author, year of publication, the country where the study was undertaken, number of samples studied from the patients with gastric cancer and the healthy controls, serum or erythrocyte SOD activity (mean \pm standard deviation), methods used to measure SOD and the units of measurement.

Quality assessment

Two independent investigators assessed the quality of each included study using the Newcastle-Ottawa Scale (NOS) for case-controlled studies. The quality score ranged from 0–9 after three items were analyzed: selection, comparability, and exposure. In the analysis, high-quality studies were defined as those that scored 7–9 points, medium-quality studies were those that scored 4–6 points, and inferior studies scored <4 points.

Statistical analysis

The meta-analysis was conducted using Stata version 12.0 (Stata Corporation, College Station, TX, USA). A P-value <0.05 was considered to be statistically significant. Because the measurement methods and units differed among the studies, the standardized mean difference (SMD) was used with a 95% confidence interval (CI) for continuous variable outcomes. Cochran Q and I^2 statistics were used to estimate inter-study heterogeneity. A random-effects model was used if the heterogeneity was significant ($p \leq 0.10$, and $I^2 > 50\%$). Otherwise,

a fixed-effects model was used. Publication bias was investigated using Egger's test (significant with $p < 0.05$). Sensitivity analysis was used to assess the impact of each independent study on the pooled SMD by omitting one study at a time. Forest plots were constructed to show the pooled data and to present the results of the included studies.

Results

Search results and quality assessment of the included studies

The database search initially identified 574 publications through the database search, and ten studies were finally identified after meeting all inclusion criteria and requirements [13–22]. The ten published studies included 1,094 subjects, 495 patients with gastric cancer and 599 healthy individuals [13–22]. Table 1 shows the baseline characteristics of these subjects included in the ten studies, which were published from 1993–2015 [13–22]. Five controlled studies [13,15,16,20,22] included an equal number of patients with gastric cancer and normal subjects who were age-matched and sex-matched and who had not undergone any treatment before providing blood samples. Among these five studies, Arivazhagan et al. [15] and Pasupathi et al. [20] enrolled only men as the study cases and controls. One study [18] was part of the Japan Collaborative Cohort Study (JACC), which included 210 participants (110 men and 100 women), in which each patient with gastric cancer had age-matched and sex-matched controls, with matched controls for age at recruitment, and research site, and with sufficient baseline blood samples were reserved for study. According to the Newcastle-Ottawa Scale (NOS) scores, five articles [13,15,18,20,22] were of high quality and five studies [14,16,17,19,21] were scored as medium quality. Table 2 shows the quality assessment results.

Outcome of meta-analysis and subgroup analysis

Meta-analysis of the ten identified studies, using the standardized mean difference (SMD) and the 95% confidence interval (CI), showed that patients with gastric cancer had significantly decreased superoxide dismutase (SOD) activity when compared with the healthy controls (SMD, -0.840 ; 95% CI, -1.463 to -0.218 ; $p = 0.008$) (Figure 2). As there was significant study heterogeneity ($I^2 = 94.4\%$, $p = 0.000$), further analysis was performed to identify the potential clinical factors contributing to the heterogeneity. For methodological and clinical quality disparity, subgroup analysis was performed based on SOD distribution in the blood and male subjects. SOD activity between the case subjects and the control groups was significantly associated in erythrocytes (SMD, -1.773 ; 95% CI, -2.504 to -1.042 ; $p = 0.000$) (Figure 3) with decreased heterogeneity

Table 1. The main baseline information of the studies included in the meta-analysis.

First author and year	Gastric cancer group			Healthy control group			Units	Measurement method	Distribution in blood	Country
	No.	Mean	SD	No.	Mean	SD				
Guo (1993) [13]	23	1446.84	216.35	23	1840.16	429.59	u/gHb	Pyrogallol autoxidation	Erythrocyte	China
Wu (1995) [14]	33	1011.53	41.53	50	1048.54	17.88	u/gHb	NBT reduction assay	Whole blood	China
Arivazhagan (1997) [15]	24	2.18	0.59	24	3.61	1.01	u/mgHb	Spectrophotometry	Erythrocyte	India
Yasuda (2002) [16]	11	15.90	7.80	11	11.30	3.30	Percent inhibition	NBT reduction assay	Serum	Japan
Sun (2004) [17]	35	6.67	0.96	16	7.85	1.10	nu/ml	ELISA	Serum	China
Yatsuya (2005) [18]	210	2.95	1.64	308	2.96	1.47	u/ml	Nitrite method	Serum	Japan
Dincer (2007) [19]	19	3.30	0.91	27	2.61	0.43	u/ml	Spectrophotometry	Serum	Turkey
Pasupathi (2009) [20]	50	2.54	0.17	50	3.21	0.36	*	NBT reduction assay	Erythrocyte	India
Lin (2014) [21]	50	78.74	31.26	50	110.32	28.73	u/ml	Xanthine oxidation	Serum	China
Maraiya (2015) [22]	40	2.15	0.82	40	3.32	0.96	Unit/mg, protein/ml	Epinephrine method	Serum	India

* One unit of activity was taken as the enzyme reaction, which gave 50% inhibition of the nitro blue tetrazolium (NBT) test. ELISA – enzyme-linked immunosorbent assay; SD – standard deviation.

Table 2. Quality assessment for the studies included in the meta-analysis.

First author and year	Selection	Comparability	Exposure	Total
Guo (1993)	***	**	**	7
Wu (1995)	**	*	***	6
Arivazhagan (1997)	***	**	**	7
Yasuda (2002)	**	**	**	6
Sun (2004)	**	**	**	6
Yatsuya (2005)	****	**	**	8
Dincer (2007)	***	*	**	6
Pasupathi (2009)	****	**	**	8
Lin (2014)	***	*	**	6
Maraiya (2015)	****	**	**	8

($I^2=77.5\%$, $p=0.012$). Heterogeneity was also significantly decreased ($I^2=56.4\%$, $p=0.130$) (Figure 4) for male subjects (SMD, -2.090 ; 95% CI, -2.725 to -1.456 ; $p<0.001$) [15,20].

Sensitivity analysis

Sensitivity analysis was conducted to evaluate the impact of individual studies on the pooled SMD when one study at a time

was omitted. Consistently, there was no significant change to the pooled estimate (Figure 5).

Publication bias

Egger's test did not identify publication bias for the association of blood SOD activity between the study cases and controls ($p=0.153$) (Figure 6).

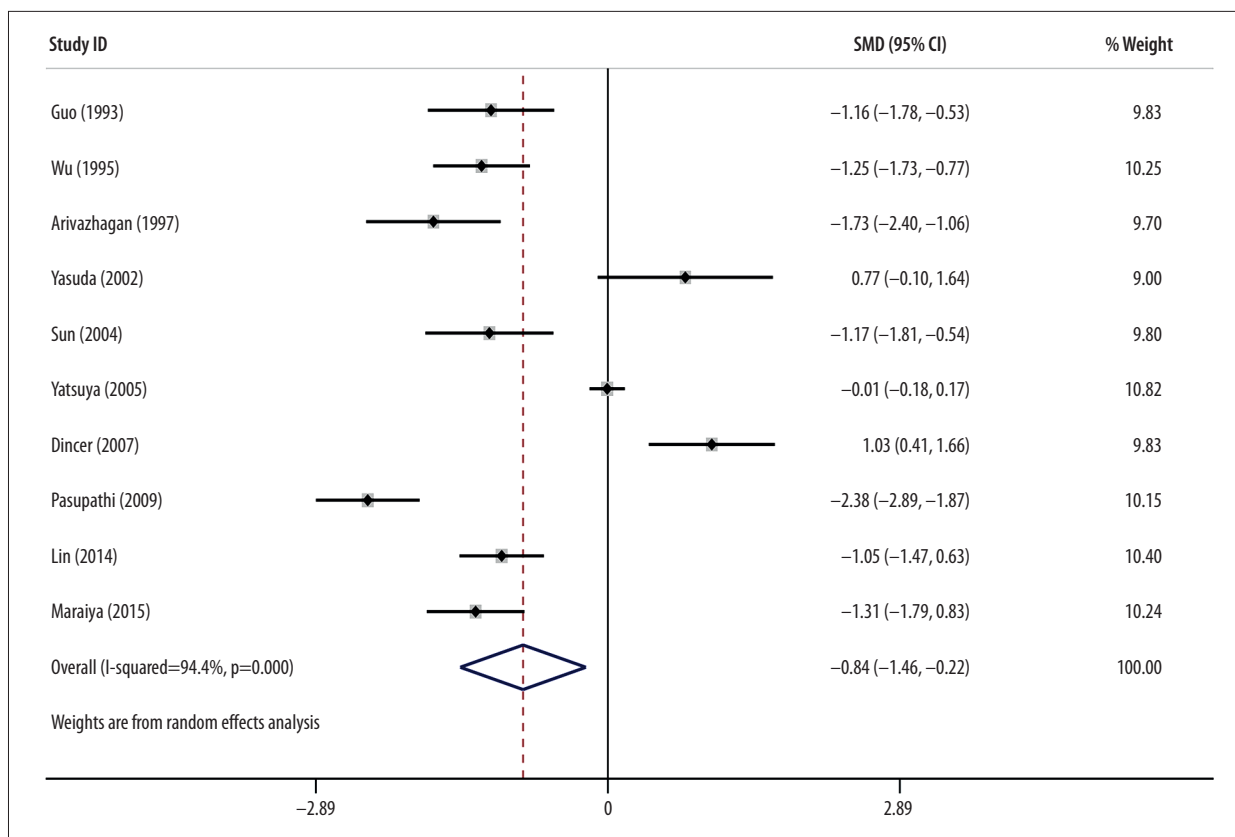


Figure 2. Forest plot of the ten published studies included in the meta-analysis [13–22].

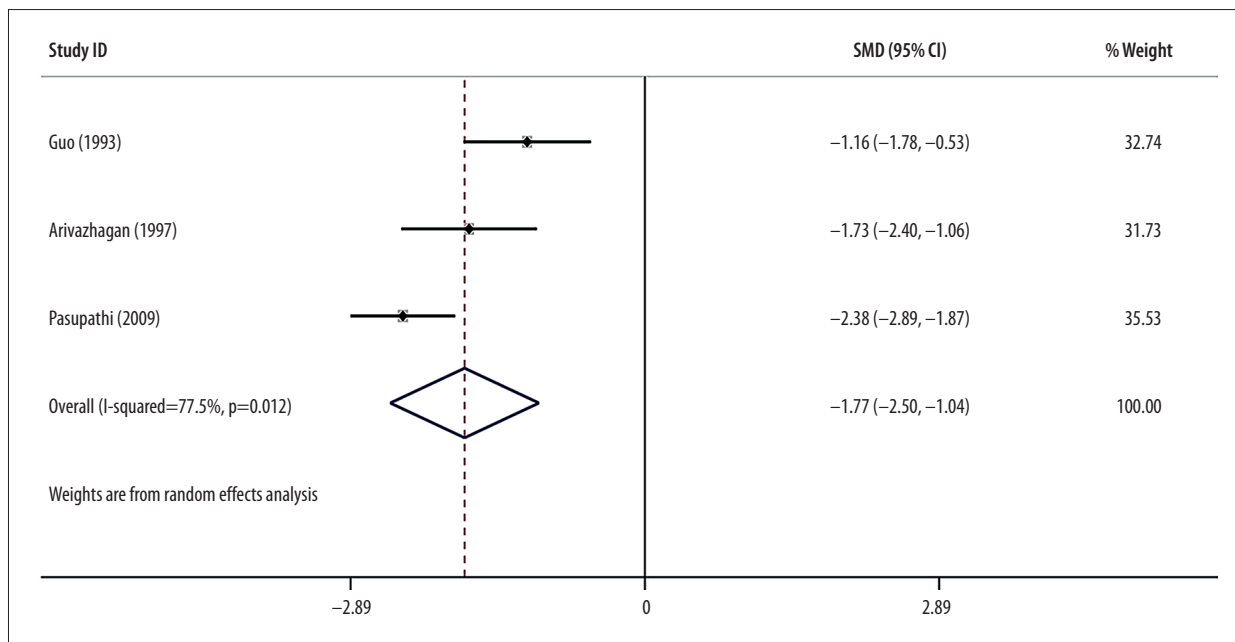


Figure 3. Forest plot of the subgroup analysis shows a significant distribution of superoxide dismutase (SOD) in erythrocytes in patients with gastric cancer compared with normal controls.

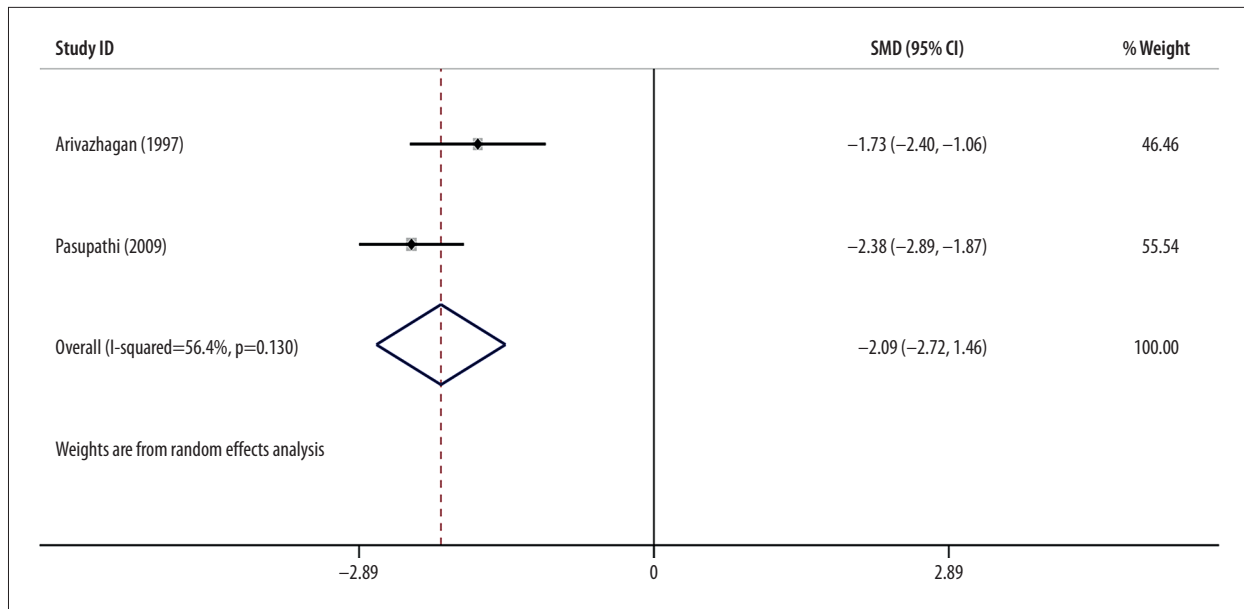


Figure 4. Forest plot of the subgroup analysis shows a significant distribution of superoxide dismutase (SOD) in male patients with gastric cancer compared with normal controls.

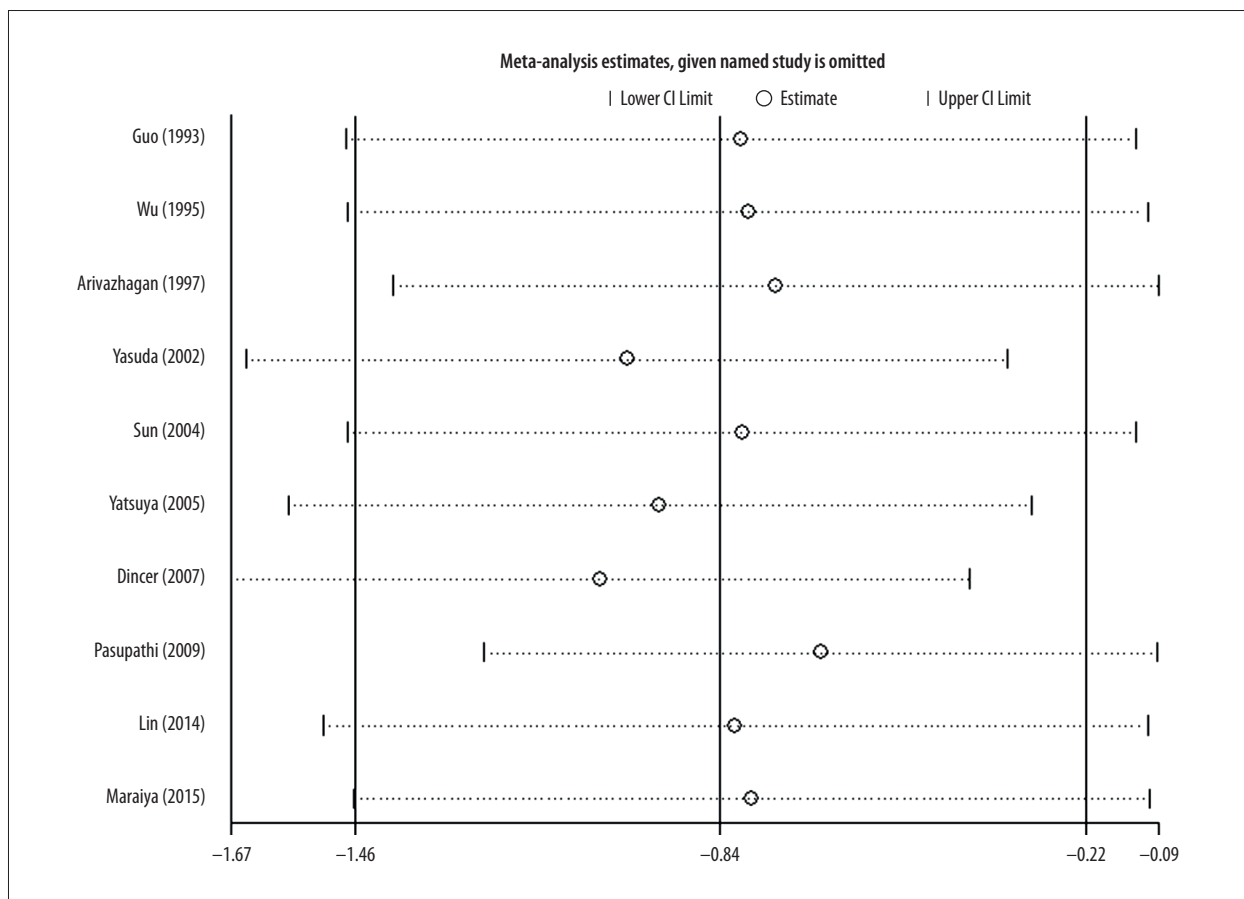


Figure 5. Sensitivity analysis estimate based on the pooled standardized mean difference (SMD), performed by omitting one study at a time.

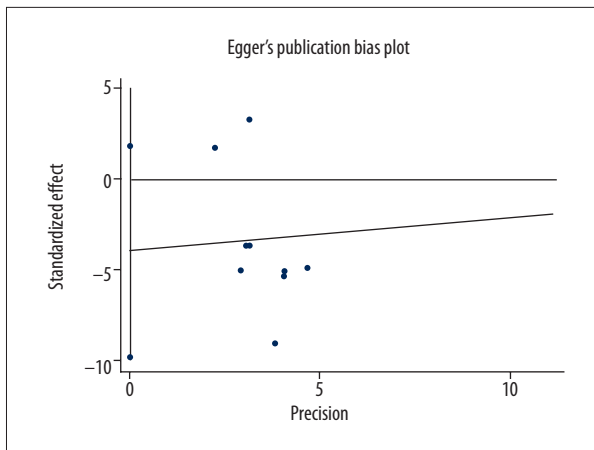


Figure 6. Egger's plot of publication bias.

Discussion

A systematic literature review on the measurement of superoxide dismutase (SOD) activity in patients with gastric cancer identified ten controlled clinical studies that included 1,094 subjects, 495 patients with gastric cancer and 599 healthy individuals [13–22]. Six studies measured SOD in serum, three studies measured SOD in erythrocytes, and one study measured SOD on whole blood. Meta-analysis showed that patients with gastric carcinoma had decreased blood-based SOD activity when compared with normal control individuals. Subgroup analysis by blood distribution and gender showed more significant results for measurement of SOD in erythrocytes and for male patients. The findings of this study indicate that SOD activity may be used as an auxiliary biochemical indicator in the detection, monitoring, or prognosis of gastric cancer. The findings of this study are supported by those of Kadir et al., who showed that tissues from gastric cancer had significantly reduced levels of SOD activity when compared with normal gastric tissue and proposed that the reduced antioxidant activity may be a prognostic marker for gastric cancer [23].

In the present study, when compared with the healthy controls, the red blood cell count and the hemoglobin levels were significantly lower in patients with gastric cancer [13,15,20]. Decreased levels of antioxidants that result in increased osmotic fragility may explain this finding. It has previously been reported that there was no significant difference in SOD activity between patients with gastritis and normal individuals [17], which may mean that the function of SOD can be physiologically regulated.

SOD has been shown to be associated with the development and progression of malignancy, but there is a need for further studies to determine the mechanisms that lead to changes in enzyme activity. Dincer et al. [19] proposed that the change in energy metabolism and the production of oxygen-derived free

radicals from dysfunctional mitochondria in malignant gastric neoplasms affect SOD activity and that decreased enzyme activity could be interpreted partly as altered expression of the genes encoding SODs during tumorigenesis. Increased ROS generation, resulting from either an external stimulus or abnormal tissue function, might cause the accumulation of SOD as a physiological protective response. Also, Yasuda et al. [16] proposed that SOD activity might reflect resistance to oxidation, as they showed that the same type of advanced-stage gastrointestinal tumor in elderly patients had much lower SOD activity than younger patients. However, other study authors have proposed that trace elements could be responsible for the change in SOD activity and have hypothesized that reduced copper and zinc trace elements in gastric tumors cause decreased SOD activity [17].

Because the SOD activity level represents cellular antioxidant ability, normal cell growth, differentiation, and physiological function depend on the balanced environments of oxidation and antioxidants, and the oxidation resistance capacity reflects the physiological status of the cells or tissues [24,25]. Currently, there is increasing evidence that chronic gastritis due to *Helicobacter pylori* infection is a risk factor for gastric dysplasia and gastric cancer. The neutrophil infiltrates associated with gastritis generate local reactive oxygen metabolites, ammonia, phospholipases, and cytotoxins [26]. Chronic gastritis associated with cell regeneration may lead to dysplasia and cancer following long-term stimulation. Detection and evaluation of the activity of SOD have become of increasing interest in the diagnosis of patients with gastric cancer due to *H. pylori* infection [27].

Currently, the diagnosis of gastric cancer relies on endoscopy and biopsy for histology. Endoscopic diagnosis of early gastric cancer requires trained endoscopists and the use of endoscopic equipment [28]. Although serum pepsinogen and serum gastrin have been reported as potential screening biomarkers for gastric cancer, serum pepsinogen is found in patients with atrophic gastritis [29], and serum gastrin also reflects antral mucosa atrophy, these methods can identify high-risk populations rather than cancer itself [30], and the final diagnosis still relies on the use of endoscopy. In some settings, evaluation of serum enzyme activity might be an option for the identification of high-risk groups. Other studies have indicated that the evaluation of serum carcinoembryonic antigen (CEA), carbohydrate antigen (CA) 19-9, and CA72-4 [31] are the most useful biochemical markers for patient follow-up to detect recurrent gastric cancer after initial surgery and chemotherapy. However, these markers have not been shown to be able to detect early gastric cancer, where measurement of SOD in the peripheral blood might be used in combinations with other biomarkers in the prognosis of gastric cancer and to detect recurrence of gastric cancer. The blood-based detection of SOD

is simple and easy to perform and might be used routinely for the detection of gastric cancer and for monitoring its progression. Also, the results of SOD activity should take into account the patient's recent intake of antioxidant vitamin supplements, such as vitamins E and C.

Reduced levels of SOD activity have been found in other diseases. Bakacak et al. [32] showed that SOD levels were significantly lower in pregnant women with pre-eclamptic compared with non-pregnant women or healthy pregnant women, which might reflect lipid peroxidation. Lewandowski et al. [33] reviewed the literature and found that decreased SOD activity had been reported in inflammatory bowel disease, obesity, diabetes mellitus, hypertension, and chronic obstructive pulmonary disease (COPD). There are several *SOD1* and *SOD3* gene polymorphisms that have been shown to be associated with the risk of developing disease, or experiencing a disease exacerbation [33]. Noor et al. [34] showed that SOD activity decreased in familial amyotrophic lateral sclerosis (ALS), Parkinson's disease, Alzheimer's disease, dengue fever, cancer, Down's syndrome, cataract, and several neurological disorders. Mutations in the *SOD1* gene can partly explain these association, but the exact mechanism remains unknown. Kang [35] reported that *SOD2* gene polymorphisms were associated with the development of non-Hodgkin lymphoma, lung cancer, and colorectal cancer, which suggested that *SOD2* gene polymorphism might be candidate markers of cancer.

This study had several limitations. First, the studies included in the meta-analysis used different methods to measure SOD activity and clinical outcome, which limited the ability to compare the differences between studies and meant that an acute threshold could not be proposed. Therefore, an optimal testing method would be ideal to help quantify the metrics. Second, there was significant heterogeneity across the studies, and the results should be interpreted with caution. Some studies that

included participants unmatched for gender and age could be the reason for the heterogeneity, as the elderly tend to have weaker antioxidant systems, and men might have been smokers or could have consumed excessive amounts of alcohol. Also, the data analysis did not include different types of gastric cancer, and meta-analysis that includes the gastric cancer type may partly clarify some of the differences among the studies [25]. Lastly, as most of the studies were observational studies of short duration, confounders may have been overlooked, and so further long-term, large-scale controlled clinical studies are required.

Conclusions

Meta-analysis has shown that patients with gastric cancer have lower superoxide dismutase (SOD) activity compared with healthy individuals. SOD activity in the blood, especially in erythrocytes, might be considered as a biochemical marker that may be used to support the diagnosis and monitoring of gastric cancer. The findings of this meta-analysis require support with large-scale, long-term controlled clinical studies with longer duration patient follow-up, to determine the clinical application of a blood-based test for SOD activity as a biomarker of gastric cancer.

Acknowledgments

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Conflict of interest

None.

Supplementary Table

Supplementary Table 1. The preferred reporting items for systematic reviews and meta-analyses (PRISMA) 2009 checklist [12].

Section/topic	#	Checklist item	Reported on page #
		Title	1
Title	1	Identify the report as a systematic review, meta-analysis, or both	1
		Abstract	2
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number	2

Section/topic	#	Checklist item	Reported on page #
Introduction			3–4
Rationale	3	Describe the rationale for the review in the context of what is already known	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)	3–4
Methods			4–6
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	4–5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means)	5–6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I ²) for each meta-analysis	5–6
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies)	5–6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified	5–6
Results			6–7
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations	6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12)	6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot	6–7
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency	7
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15)	7

Section/topic	#	Checklist item	Reported on page #
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16])	7
Discussion			7–10
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8–10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias)	10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research	10
Funding			1
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review	1

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med* 6(7): e1000097. doi: 10.1371/journal.pmed1000097. For more information, visit: www.prisma-statement.org.

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