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REVIEW

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Malondialdehyde (MDA) and 8-hydroxy-2′-deoxyguanosine (8-OHdG) in ischemic stroke: a systematic review

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Abstract

Introduction The low blood flow in ischemic stroke reduces oxygen and glucose and induces a series of reactions that produce free radicals. Free radicals can destroy cell membranes (lipid peroxidation) marked by the elevation of malondialdehyde (MDA), and the damage of deoxyribonucleic acid (DNA) showed by the elevation of 8-hydroxy-2′-deoxyguanosine (8-OHdG). This review aimed to assess and conclude the research-based study systematically to analyze the relationship of MDA/8-OHdG and ischemic stroke.

Method Cochrane handbook for systematic reviews, the guideline of preferred reporting items for systematic review and meta-analysis (PRISMA), and synthesis without meta-analysis (SWiM) in systematic reviews: reporting guideline was used as guideline in this systematic review. Inclusion criteria in this review were primary studies of every design, articles published in English around January 2000–December 2021, and the study used human as subject. A systematic literature search was applied in 15 electronic medical journals. The authors assessed the study quality and risk of bias of each included study.

Results The authors evaluated 374 studies found in literature searching, 30 studies met the criteria for this review, and then underwent the assessment of study quality and risk of bias.

Conclusion MDA has the role as oxidative stress biomarker, outcome predictor, mortality predictor, post-stroke cognitive impairment predictor, post-stroke depression predictor, and hand grip strength predictor of ischemic stroke; while 8-OHdG has the role as oxidative stress biomarker, outcome predictor, mortality predictor, post-stroke cognitive impairment predictor, post-stroke depression predictor of ischemic stroke.

Keywords 8-OHdG, Ischemic stroke, MDA

Introduction

Stroke is a significant contributor to morbidity, disability, and mortality in the world [1–3]. American Heart Association (AHA) reported the mortality rate of stroke increased about 0.7 per 100.000 from 2010 to 2016 in 35–64 years of age; while Centers for Disease Control and Prevention (CDC) reported that every 4 min someone dies due to stroke, and stroke also reduces mobility in more than 50% of stroke geriatric survivors [4, 5]. Ischemic stroke is the frequent stroke

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(approximately 80% of stroke) caused by impaired perfusion to the brain [4–8].

Oxidative (and nitrosative) stress is described as a disproportion of pro-oxidants (such as free radicals) and antioxidants, which has been associated with the pathogenesis of several chronic disorders such as ischemic stroke due to the dysfunction of blood–brain barrier (BBB) and neuronal degeneration and apoptosis [9–11]. Oxidative (and nitrosative) stress has an essential role in ischemic stroke through several actions. The low blood flow in ischemic stroke reduces the oxygen and glucose and induces a series of reactions that produce free radicals (reactive oxygen species (ROS) and reactive nitrogen species (RNS)). Free radical has various roles including as a part of vascular regulatory system, oxygen pressure monitoring, and erythropoietin generation in small levels, but abundant levels of free radicals may oxidize macromolecules and lead to lethal cell damage (neuronal death and brain edema) [9–12]. Excitotoxic injury induces superoxide and nitric oxide (NO) generation, inducing the production of highly reactive products, including peroxynitrite and hydroxyl radicals, which can destroy lipids, proteins, and DNA [13]. The brain is particularly endangered to oxidative stress because of the high level of fatty acids cell membranes, its high rate of oxidative metabolic activity and potent generation of free radical (basal oxygen consumption), lower neuronal antioxidant capacity, and elevated concentration of iron (which acts to catalyze the conversion of H_2O_2 to highly reactive hydroxyl radicals) [14–16].

Free radicals can damage cell membrane (lipid peroxidation) marked by the elevation of malondialdehyde (MDA), and the damage of deoxyribonucleic acid (DNA) showed by the elevation of 8-hydroxy-2′-deoxyguanosine (8-OHdG). MDA is one of the aldehyde molecules product due to the breakage of polyunsaturated fatty acids chains in the cell membrane, while 8-OHdG is formed by the interaction of free radicals and guanine (nitrogen base in DNA) [17]. Haritha et al. (2020) reported the elevation of MDA level in ischemic stroke, while Elsayed et al. (2020) reported the correlation of MDA level and clinical outcome of ischemic stroke [18, 19]. Syafrita et al. (2020) reported that MDA and 8-OHdG were associated with depression post-stroke [10]. The role of biomarker in ischemic stroke is important, especially in hospitals with limited neuroimaging facilities.

MDA and 8-OHdG in ischemic stroke have been presented in different studies, but a systematic review about this topic was not available. The current systematic review aimed to evaluate and conclude the research-based study systematically to assess the relationship of MDA/8-OHdG and ischemic stroke.

Methods

This study's protocol was recorded on International Prospective Register of Systematic Reviews (PROSPERO) (CRD42022289876). This review was conducted in accordance to Cochrane handbook for systematic reviews and the guideline of preferred reporting items for systematic review and meta-analysis (PRISMA) [20, 21]. The data collection and analysis (synthesis) were also conducted based on synthesis without meta-analysis (SWiM) in systematic reviews: reporting guideline [22].

Inclusion and exclusion criteria

Inclusion criteria:

1. Publication type:

- full-text manuscripts reported the relationship of MDA/8-OHdG and ischemic stroke
- Experimental study (clinical trial) and observational study [descriptive study (case report and case series) and analytical studies (cross-sectional, case–control, and prospective study)]

2. Articles published in English
3. Articles published in January 2000–December 2021
4. The study used human as subject
5. Objective, methodology, and outcome of study must discuss the relationship of MDA/8-OHdG and ischemic stroke.

Exclusion criteria:

1. Publication type was review
2. Variables that were associated with the relationship of MDA/8-OHdG and ischemic stroke.

Literature search

A systematic literature searching was used in these online medical bibliographic databases: Cambridge Core, Clinical Key, Cochrane, Ebsco, Embase, Emerald Insight, Google Scholar, JSTOR, Medline, Nature, Proquest, Pubmed, Science Direct, Scopus, and Springer Link. The search was performed using the following keywords for the title and abstract: (malondialdehyde OR MDA OR 8-hydroxy-2′-deoxyguanosine OR 8-OHdG OR 8-oxo-7,8-dihydro-2′-deoxyguanosine OR 8-OHdG) AND (ischemic stroke OR infarct stroke OR thrombotic stroke

OR embolic stroke). The references from included studies were evaluated to avoid the loss of any published article.

Data collection and analysis

Articles were chosen for assessment after two authors (DT and AP) had checked keywords from the online medical bibliographic databases. The results of the literature search were deliberated with third author (RR), and any discrepancies of results were discussed. Selected full-papers were independently evaluated by the other authors (YA and AK). Selected articles for this systematic review were checked by two authors independently to confirm the results (RA and JB). The data from included articles were provided in a summary table, containing key points of each study. The key points of each study were: first author and country; study design; sample characteristic; management/outcome measure; and outcome/result.

Quality assessment

The first author assessed the study quality and risk of bias of each retrieved article and discussed them with other authors. Newcastle–Ottawa scale for prospective study was used to evaluate the quality and risk of bias of prospective study; interpretation of total score was: ≥ 7 points were considered in good studies, 5–6 points were considered in fair studies, < 5 points were considered in poor studies. Newcastle–Ottawa scale for case control study was applied to assess case control study; interpretation of total score was: ≥ 7 points were included in good studies, 5–6 points were included in fair studies, < 5 points were included in poor studies. Newcastle–Ottawa scale adapted for cross-sectional study was used to evaluate the quality and risk of bias of the cross-sectional study. Interpretation of total score was: 9–10 points were included in very good studies, 7–8 points were included in good studies, 5–6 points were included in satisfactory studies, and 0–4 points were included in unsatisfactory studies [23–27].

Results

Selection of articles for review

Figure 1 provides PRISMA flow diagram. At first, 364 peer-reviewed studies were found from online databases and an additional 10 studies were identified through other sources (search engine). After duplicates were eliminated, 212 studies remained for the title and abstract screening. Articles that did not meet the inclusion and exclusion criteria were not evaluated. Thirty-six articles were evaluated for eligibility of which 30 articles were included in this review.

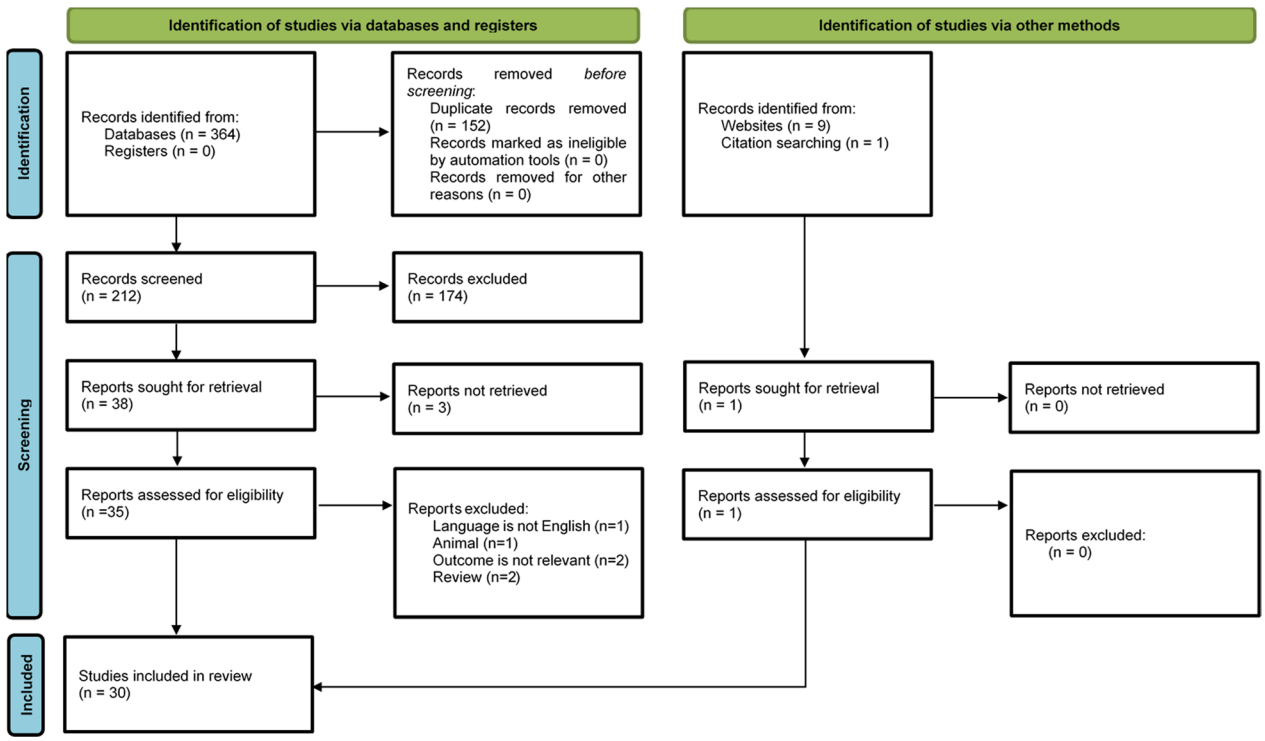

Fig. 1 PRISMA flow diagram

Table 1 Newcastle–Ottawa scale (prospective study)

No.	First author, year	Selection				Comparability	Outcome			Total
		1	2	3	4		1	2	3	
1.	Atiba, 2020 [28]		*	*	*	**	*	*	*	9
2.	Aygul, Turkey, 2008 [29]		*	*	*	**	*	*	*	8
3.	Cano, 2003 [30]		*	*	*	**	*	*	*	8
4.	Cojocaru, 2013 [31]		*	*	*	**	*	*	*	8
5.	Dominguez, 2010 [32]		*	*	*		*	*	*	6
6.	Elsayed, 2020 [18]		*	*	*		*	*	*	7
7.	Liu, 2017 [17]	*	*	*	*	*	*	*	*	8
8.	Liu, 2018 [11]		*	*	*	**	*	*	*	9
9.	Lorente, Spain, 2015 [33]		*	*	*	**	*	*	*	8
10.	Lorente, Spain, 2016 [34]		*	*	*	**	*	*	*	8
11.	Lorente, 2021 [35]		*	*	*	**	*	*	*	9
12.	Lorenzano, 2018 [36]	*	*	*	*	**	*	*	*	9
13.	Mizukoshi, 2005 [37]			*	*		*	*	*	5
14.	Nakajima, 2012 [12]			*	*		*	*	*	5
15.	Polidori, 2002 [38]		*	*	*	**	*	*	*	8
16.	Tsai, 2014 [39]		*	*	*	**	*	*	*	8
17.	Zimmermann, 2004 [40]		*	*	*	**	*	*	*	8

Maximum point for comparability was 2

Selection: (1) representativeness, (2) selection of non-exposed, (3) ascertainment of exposure, (4) demonstration that outcome was not present at the beginning

Outcome: (1) assessment of the outcome, (2) follow-up long enough, (3) adequacy of follow-up

The sign of * meant the point that each article was got

Assessment of study validity (quality assessment and risk of bias)

All included articles were associated to MDA/8-OHdG and ischemic stroke. Table 1 presents quality scores for prospective studies and the studies had 5–9 points (fair and good study). Table 2 presents quality scores for case–control studies and the studies had 8–9 points (good study). Table 3 presents quality scores for cross-sectional studies and all of the studies had 8 points (good study).

Study characteristic

The study characteristics for the included studies are shown in Table 4. Most of the studies were prospective studies and discussed about oxidative stress biomarker of acute ischemic stroke (AIS).

Discussion

The role of oxidative stress in ischemic stroke

AIS induces the generation of free radicals through various mechanisms, including the stimulation of N-methyl-D-aspartate (NMDA) receptors, induction of neuronal nitric oxide synthase or cyclooxygenase (COX)

Table 2 Newcastle–Ottawa scale (case–control study)

No.	First author, year	Selection				Comparability	Exposure			Total
		1	2	3	4		1	2	3	
1.	Milanlioglu, 2016 [16]	*		*	*	**	*	*	*	8
2.	Menon, 2020 [14]	*		*	*	**	*	*	*	8
3.	Shaafi, 2021 [9]	*	*	*	*	**	*	*	*	9
4.	Syafrita, 2020 [10]	*		*	*	**	*	*	*	8

Maximum point for comparability was 2

Selection: (1) case definition, (2) representativeness, (3) selection of controls, (4) definition of controls

Exposure: (1) ascertainment of exposure, (2) method

The sign of * meant the point that each article was got

Table 3 Newcastle–Ottawa scale adapted for cross-sectional study

No.	First author, year	Selection				Comparability	Outcome		Total
		1	2	3	4		1	2	
1.	Aygul, 2006 [13]		*	*	**	**	*	*	8
2.	Bir, 2006 [41]		*	*	**	**	*	*	8
3.	Demirkaya, 2001 [42]		*	*	**	**	*	*	8
4.	Dogan, 2018 [43]		*	*	**	**	*	*	8
5.	Haritha, 2020 [19]		*	*	**	**	*	*	8
6.	Moon, 2014 [44]		*	*	**	**	*	*	8
7.	Mueangson, 2020 [45]		*	*	**	**	*	*	8
8.	Sarkar, 2009 [46]		*	*	**	**	*	*	8
9.	Yildirim, 2007 [47]		*	*	**	**	*	*	8

Maximum points for selection number 4, comparability, and outcome number 1 were 2

Selection: (1) representativeness of the sample, (2) sample size, (3) non-respondents, (4) risk factor measurement tool

Outcome: (1) assessment of the outcome, (2) statistical test

The sign of * meant the point that each article was got

2, auto-oxidation of catecholamines metabolism of free fatty acids during ischemia, the generation of xanthine dehydrogenase to xanthine oxidase, mitochondrial impairment, and BBB disruption that cause migration of neutrophils and leukocytes [31, 39, 49].

O_2^-, H_2O_2, OH^- are the principal route of the generation of ROS through the reduction of molecular oxygen. Oxidative stress is the result of uncontrolled ROS formation because of oxygen metabolism, oxygen reperfusion injury from hypoxic condition, and also hemoglobin and myoglobin oxidation. The condition of free radicals will cause the brain to consume more lipid, increases oxygen demand, and induces the oxidation of dopamine and glutamate. Additionally, the level of catalase enzyme in the neurons will decline, causing impairment of glutathione peroxidase ability to eradicate H_2O_2. ROS is a hazardous final product of oxidative phosphorylation and reperfusion injury, because it could cause cellular redox which will affect the activity of protein–protein bond and DNA–protein bond of certain enzymes and transcription factors [50]. The other effects of ROS actions are altered function of receptors, ion channels, and other membrane proteins; that damage cell membrane fluidity and permeability, cause lipid peroxidation, protein denaturation, nucleic acid and DNA damage, damage to cytoskeletal structure, and chemotaxis [49, 51]. When brain contains abundant polyunsaturated fatty acids, ROS could easily elevate lipid peroxidation. Lipid peroxidation can also be activated by non-radical ROS, especially in acidic conditions, including during ischemic stroke. Lipid peroxidation can change membrane instability and permeability, as well as the function of ion pumps on the membrane border. This condition will endanger ion homeostasis, and can lead to loss of membrane integrity and cell injury. Lipid peroxidation can also induce disintegration of pro-inflammatory isoprostanoid mediator which is highly dangerous and release strong oxidant like 4-hydroxynonenal (4-HNE) [50].

The importance of oxidative stress in ischemic stroke pathophysiology make the use of antioxidants became pivotal to provide protection from neurological impairment. Oxidative stress states occur when cellular antioxidant defenses are inadequate to sustain the level of free radicals under a lethal threshold. This may be due to uncontrolled generation of free radicals or the failure of antioxidant defenses, or both [44, 47]. The extensive lesion of oxidative stress damage is also dependent on the antioxidant defense mechanism (including antioxidant enzymes such as SOD, catalase, and glutathione peroxidase; and antioxidant non-enzymatic such as retinol, ascorbic acid, α-tocopherol, carotenoid, and uric acid) [18, 39]. In severe stroke, antioxidants cannot balance the huge free radicals due to the larger neurological damage lesion. The antioxidant enzymes are inducible enzymes, so the transcription and production take time [18]. Agents that can prevent or decrease the effect of oxidative stress and reduce the number of cell damage in stroke are called neuroprotective drugs, such as edaravone, tirilazad, citicoline, etc. [50, 52].

MDA and 8-OHdG in ischemic stroke

There were 30 studies that reported the use of MDA and 8-OHdG as ischemic stroke biomarkers. MDA and 8-OHdG were commonly used as biomarkers of oxidative stress in various diseases including stroke. They were the final result of oxidative stress process because of the degradation of cellular organelles. After the release of MDA

Table 4 Study characteristic

No.	First author, country, year	Study design	Sample (n)	Sample characteristic: age (year), gender (male, female)	Outcome measure	Result
1.	Aygul, Turkey, 2006 [13]	Cross-sectional	AIS: 19 Healthy: 20	AIS Age: 64.7 ± 7.9 Gender: 11, 8 Healthy Age: 62.5 ± 8.3 Gender: 12, 8	Oxidative stress biomarker of AIS	CSF MDA level in IS group was significantly higher than control group (16.5 ± 3.5 vs 14.4 ± 3.4 nmol/mL, $p < 0.05$)
2.	Aygul, Turkey, 2008 [29]	Prospective study	IS: 29 Healthy: 13	IS Age: 61. 9 ± 10. 4 Gender: 12, 17 Healthy Age: 58.1 ± 6.8 Gender: 6, 7	Oxidative stress biomarker of IS	MDA level in IS group within 3–4 d after onset was significantly higher than control group (14.3 vs 10.6 µmol/L, p: .004)
3.	Bir, Turkey, 2006 [41]	Cross-sectional	IS Atherothrombotic: 19 Lacunar: 19 Healthy: 30	Atherothrombotic Age: 69 (38–79) Gender: 10, 9 Lacunar Age: 58 (30–79) Gender: 10, 9 Healthy Age: 59 (40–69) Gender: 16, 14	Oxidative stress biomarker of chronic IS	MDA level in chronic IS (athero-thrombotic & lacunar) was significantly higher than control group (3.5 vs 1.69 nmol/mL, $p < 0.001$; 3.83 vs 1.69 nmol/mL, $p < 0.001$)
4.	Cano, Venezuela, 2003 [30]	Prospective study (24 h)	AIS: 15 Healthy: 15	AIS Age: 64 ± 3.6 Gender: 8, 7 Healthy Age: 56.7 ± 1.3 Gender: 8, 7	Oxidative stress biomarker of AIS (thrombotic stroke)	MDA level in AIS within 24 h after onset was significantly higher than control group (47.9 ± 7.1 vs 1.7 ± 0.2 µmol/L, $p < 0.001$)
5.	Chen, China, 2018 [48]	Cross-sectional	PSD: 70 Non-PSD: 69	PSD Age: 65.8 (55.9–74.2) Gender: 48, 22 Non-PSD Age: 59.7 (53.6–72.1) Gender: 49. 20	PSD predictor	Urinary 8-OHdG level in PSD group was insignificantly higher than control group (40.1 vs 38.6 ng/mgCr, p: 0.056). Urinary 8-OHdG level was positively correlated with PSD (r: 0.202, p: 0.017)
6.	Cojocaru, Romania, 2013 [31]	Prospective study (7 d)	AIS: 57 Healthy: 51	AIS Age: 73.4 ± 6.5 Gender: 33, 24	Oxidative stress biomarker of AIS	MDA level in AIS within 24 h and 7 d after onset was significantly higher than control group (2.36 vs 1.32, $p < 0.05$; 3.14 vs 1.32, $p < 0.001$)

Table 4 (continued)

No.	First author, country, year	Study design	Sample (n)	Sample characteristic: age (year), gender (male, female)	Outcome measure	Result
7.	Demirkaya, Turkey, 2001 [42]	Cross-sectional	AIS: 34 Healthy: 30	AIS Age: 59.3 ± 12.6 Gender: 20, 14 Healthy Age: 54.4 ± 8.7 Gender: 19, 11	Oxidative stress biomarker of AIS, outcome predictor	MDA level within 1 day after AIS onset was higher significantly than control group (349.7 ± 60.5 vs 200 ± 65.7 mol/gHb, $p < 0.001$). Higher MDA level within 1 day was significantly associated with infarct size, stroke severity, poor short-term clinical outcome, and prognosis (r: 9.964, $p < 0.001$; r: 0.846, p: 0.004; r: 0.557, $p < 0.001$; p: 0.021)
8.	Dogan, Turkey, 2018 [43]	Cross-sectional	IS: 20 IS risk: 22 Healthy: 27	IS Age: 64.2 ± 14.04 Gender: 11, 9 IS risk Age: 59.2 ± 8.74 Gender: 12, 10 Healthy Age: 12, 15 Gender: 59.1 ± 12.09	Oxidative stress biomarker of IS	MDA level in IS group was significantly higher than control group ($p < 0.05$)
9.	Dominguez, Spain, 2010 [32]	Prospective study (24 h)	AIS: 160 Healthy: 60	AIS Age: 74 (65–78) Gender: 88, 72	Oxidative stress biomarker of AIS	MDA level in AIS group was significantly higher than control group (1.13 ± 0.33 vs 0.69 ± 0.24 µmol/L, $p < 0.01$) and significantly increased within hours (1, 2, 12, 24 h; $p < 0.001$). Higher MDA level in AIS group was associated with stroke severity, clinical outcome, and hemorrhagic complications ($p < 0.05$)
10.	Elsayed, Egypt, 2020 [18]	Prospective study (3 mo)	AIS: 42	Age: 62.95 ± 4.21 Gender, 20, 22	Functional outcome predictor	Higher MDA level was significantly correlated with mRS score (r: 0.54, p: 0.001)
11.	Haritha, India, 2020 [19]	Cross-sectional	IS: 60 Healthy: 30	IS Age: 55.95 ± 7.98 Gender: 39, 21 Healthy Age: 56.20 ± 7.48 Gender: 20, 10	Oxidative stress biomarker of IS	MDA level in IS group was significantly higher than control group (5.18 ± 1.26 vs 3.27 ± 1.26, $p < 0.001$)

Table 4 (continued)

No.	First author, country, year	Study design	Sample (n)	Sample characteristic: age (year), gender (male, female)	Outcome measure	Result
12.	Liu, China, 2017 [17]	Prospective study (30 d)	PSCI: 101 Non-PSCI: 92	PSCI Age: 66 (56–72) Gender: 56, 45 Non-PSCI Age: 65, 27 Gender: 60 (52.3–65.8)	PSCI predictor	MDA and 8-OHdG level in PSCI group were significantly higher than control group (3.6 vs 2.3, $p < 0.001$; 217.5 vs 159.4, $p < 0.001$). MDA (> 2.59 nmol/ml) and 8-OHdG (> 158.63 ng/L) level were associated with PSCI ($p < 0.05$)
13.	Liu, China, 2018 [11]	Prospective study (30 d)	PSD: 70 Non-PSD: 171	PSD Age: 64 (57–71) Gender: 45, 25 Non-PSD Age: 64 (56–70) Gender: 110, 61	PSD predictor	8-OHdG level in PSD group was significantly higher than control group (218 vs 164.8 ng/L, $p < 0.001$). 8-OHdG level (≥ 200 ng/L) was positively correlated with PSD (r: 0.129, p: 0.046)
14.	Lorente, Spain, 2015 [33]	Prospective study (30 d)	IS non-survivor: 26 IS survivor: 24 Healthy: 100	IS non-survivor Age: 66 (45–76) Gender: 17, 9 IS survivor Age: 47 (32–67) Gender: 16, 8 Healthy Age: 59 (47–71) Gender: 62, 38	Oxidative stress biomarker of IS, mortality predictor	MDA level in IS group was significantly higher than control group (2.16 vs 1.11, $p < 0.001$), and in non-survivor group was significantly higher that survivor group (2.95 vs 1.83, $p < 0.001$). Higher MDA level (> 2.27 nmol/mL) was associated with 30-day mortality of IS patients (OR: 7.23, 95% CI: 1.84–28.73, p: 0.005)
15.	Lorente, Spain, 2016 [34]	Prospective study (30 d)	Non-survivor: 29 Survivor: 29	Non-survivor Age: 64 (54–70) Gender: 18, 11 Survivor Age: 57 (47–67) Gender: 16, 13	Mortality predictor	MDA level in non-survivor group was significantly higher than survivor group (2.93 vs 1.9 nmol/mL, p: 0.004)
16.	Lorente, Spain, 2021 [35]	Prospective study (30 d)	Non-survivor: 34 Survivor: 34	Non-survivor Age: 63 (53–70) Gender: 21, 13 Survivor Age: 59 (47–68) Gender: 20, 14	Mortality predictor	8-OHdG level in non-survivor group was significantly higher than survivor group (6 vs 3.86, $p < 0.001$). Higher 8-OHdG level (> 4.82 ng/mL) was associated with 30-day mortality of IS (OR: 1.568, 95% CI: 1.131–2.174, p: 0.01)

Table 4 (continued)

No.	First author, country, year	Study design	Sample (n)	Sample characteristic: age (year), gender (male, female)	Outcome measure	Result
17.	Lorenzano, USA, 2018 [36]	Prospective study (9 h)	Infarct growth: 170 No Infarct growth: 50	Infarct growth Age: 69.9 ± 14.0 Gender: 107, 63 No Infarct growth Age: 67.9 ± 17.2 Gender: 23, 27	Infarct growth of AIS	8-OHdG level in infarct growth group was insignificantly higher than control group (5.6 vs 3.4 ng/mL, p: 0.18)
18.	Menon, India, 2020 [14]	Case–control	AIS: 100 Healthy: 99	AIS Age: 55.54 ± 11.57 Gender: Male 74% Healthy Age: 57.39 ± 10.53 Gender: Male 74%	Oxidative stress biomarker of AIS	MDA level in AIS group was significantly higher than control group (7.11 ± 1.67 vs 1.64 ± 0.82, $p < 0.05$)
19.	Milanlioglu, Turkey, 2016 [16]	Case–control	AIS: 45 Healthy: 30	AIS Age: 64 ± 15 Gender: 30, 15 Healthy Age: 62 ± 8 Gender: 20, 10	Oxidative stress biomarker of AIS	MDA level in AIS group within 24 h after onset was significantly higher than control group (6.77 ± 1.44 vs 5.9 ± 1.62, $p < 0.05$)
20.	Mizukoshi, Japan, 2005 [37]	Prospective study (3–5 d)	AIS: 7 Healthy: 6	AIS Age: 73 Gender: 4, 3 Healthy Age: 67 Gender: 4, 2	Oxidative stress biomarker of AIS (cardioembolic stroke)	Higher urinary 8-OHdG level within 3–5 days after onset was significantly associated with acute cardioembolic stroke ($p < 0.01$)
21.	Moon, Korea, 2014 [44]	Cross-sectional	AIS: 71 CIS: 28	AIS Age: 66.8 ± 10.7 Gender: 46, 25 CIS Age: 66.1 ± 11.1 Gender: 12, 16	Oxidative stress biomarker of IS (atherosclerotic)	Higher MDA level was significantly correlated with infarct volume of AIS (r: 0.551, $p < 0.05$)
22.	Mueangson, Thailand, 2020 [45]	Cross-sectional	IS: 91 Healthy: 91	IS Age: 69 ± 14 Gender: 59, 32 Healthy Age: 68 ± 13 Gender: 59, 32	Oxidative stress biomarker of IS, HGS biomarker	MDA level in IS group was significantly higher than control group (7.05 ± 3.49 vs 5.98 ± 5.68, p: 0.022). Higher MDA level was associated with low HGS in the non-paretic limbs of IS patients (AOR: 1.280, 95% CI: 1.024–1.6, p: 0.03)

Table 4 (continued)

No.	First author, country, year	Study design	Sample (n)	Sample characteristic: age (year), gender (male, female)	Outcome measure	Result
23.	Nakajima, Japan, 2012 [12]	Prospective study (7 d)	Lacunar: 9 Atherothrombotic: 22 Cardioembolic: 13 Poor outcome 25 Good outcome: 19	Lacunar Age: 74 Gender: 5, 4 Atherothrombotic Age: 69 Gender: 8, 14 Cardioembolic Age: 74 Gender: 7, 6 Poor outcome Age: 72 Gender: 13, 12 Good outcome Age: 70 Gender: 12, 7	Clinical outcome predictor	**Δ** 8-OHdG level (day 0 to 7) in atherothrombotic group was significantly higher than lacunar group (33.8 vs 6.3, p: 0.048). **Δ** 8-OHdG level (day 0 to 7) in poor outcome was significantly higher than good outcome (39.44 vs 2.54, p: 0.004)
24.	Polidori, Italy, 2002 [38]	Prospective study (7 d)	AIS: 28 Healthy: 76	AIS Age: 76.9 ± 8.7 Gender: 19. 9 Healthy Age: 77.3 ± 10.1 Gender: 48, 28	Oxidative stress biomarker of AIS, functional outcome predictor	MDA level in AIS group was significantly higher than control group, and was associated with clinical outcome ($p < 0.05$)
25.	Sarkar, India, 2009 [46]	Cross-sectional	IS: 100 Healthy: 100	IS Age: 70 ± 7.5 Gender: 70, 30 Healthy Age: 68.2 ± 4.1 Gender: 64, 36	Oxidative stress biomarker of IS	MDA level in IS group was significantly higher than control group (6.7 ± 0.1 vs 3.1 ± 1.6, $p < 0.001$)
26.	Shaafi, Iran, 2021 [9]	Case–control	AIS: 216 AIS risk: 152 Healthy: 188	AIS group Age: 71.76 ± 9.88 Gender: 148, 68 AIS risk Age: 71.89 ± 10.22 Gender: 88, 64 Healthy Age: 73.32 ± 9.43 Gender: 92, 96	AIS development and outcome predictor	MDA level in AIS group was significantly higher than control group (2.08 vs 1.85 µmol/L, $p < 0.05$). Higher MDA level was associated with the development of AIS ($p < 0.001$) and negatively correlated with mRS score 3 months of follow-up (p: 0.04, r: -0.26)

Table 4 (continued)

No.	First author, country, year	Study design	Sample (n)	Sample characteristic: age (year), gender (male, female)	Outcome measure	Result
27.	Syafrita, Indonesia, 2020 [10]	Case–control	PSD: 36 Non-PSD: 36	PSD Age: 59.67 ± 11.2 Gender: 19, 17 Non-PSD Age: 59.64 ± Gender: 18, 18	PSD predictor	MDA and 8-OHdG level in PSD group were significantly higher (110.06 ± 33.27 vs 99.98 ± 54.76, p 0.024; 4.39 ± 2.19 vs 3.08 ± 0.73, $p < 0.001$). MDA and 8-OHdG level were positively correlated with PSD (r: 0.268, p 0.023; r: 0.432, $p < 0.001$)
28.	Tsai, Taiwan, 2014 [39]	Prospective study (3 mo)	Small-vessel disease: 75 Large-vessel disease: 25 Control: 80	Small-vessel disease age: 61 ± 11.7 Gender: 60, 15 Large-vessel disease age: 64.6 ± 8.8 Gender: 17, 8	Oxidative stress biomarker of AIS, Outcome predictor	MDA level in AIS group was significantly higher than control group on day 1 and 7 after onset and associated with poor outcome ($p < 0.05$)
29.	Yildirim, Turkey, 2007 [47]	Cross-sectional	AIS: 32 Healthy: 18	AIS Age: 59.6 ± 10.6 Gender: 17, 15 Healthy Age: 55.7 ± 9.3 Gender: 10, 8	Oxidative stress biomarker of AIS	Serum and CSF MDA level in AIS group were significantly higher than control group (8.6 ± 1.8 vs 7.1 ± 2.1, $p < 0.01$; 5.9 ± 2.2 vs 4.2 ± 1.6, $p < 0.01$)
30.	Zimmermann, Germany, 2004 [40]	Prospective study (7 d)	IS: 11 History of IS: 17	IS Age: 62.2 ± 8.4 Gender: 6, 5 History of IS Age: 63.4 ± 7.8 Gender: 3, 14	Oxidative stress biomarker of AIS	MDA level in AIS group (within 48 h of onset) was significantly higher than control group ($p < 0.05$)

8-OHdG 8-hydroxy-2′-deoxyguanosine, *95% CI* 95% confidence interval, *AIS* acute ischemic stroke, *CIS* chronic ischemic stroke, *CSF* cerebrospinal fluid, *d* day, *h* hour, *HGS* hand grip strength, *IS* ischemic stroke, *L* liter, *mo* month, *OR* odds ratio, *p* probability, *PSCI* post-stroke cognitive impairment, *PSD* post-stroke depression, *r* correlation coefficient, *MDA* malondialdehyde, *mL* milliliter, *mRS* modified Rankin scale, *ng* nanogram

and 8-OHdG into the extracellular space, it reached the CSF and blood; therefore, it had been applied as a reliable biomarker of oxidative stress [14]. Urinary 8-OHdG was also deliberated as a pivotal biomarker of oxidative stress because oxidized DNA (8-OHdG) was water-soluble and excreted into the urine without being further metabolized [16].

The different pathophysiology of lacunar infarction (small-vessel) and large-vessel infarction stroke make the difference of MDA and 8-OHdG levels in each type. The pathogenesis of lacunar infarction is lipohyalinosis, while atherothrombosis is the major cause of large-vessel infarction; and the stress oxidative level was higher in large-vessel infarction due to the infarction volume [12, 39]. The number of risk factors in each type of ischemic stroke also affects the level of oxidative stress [12].

The lipid peroxidation due to acute ischemia; and conversion of xanthine dehydrogenase to xanthine oxidase and protein kinase activation (due to the activation of phospholipase and protease because of the elevation of cytosolic calcium) are the main cause of MDA elevation in AIS [9, 31, 39, 49]. The reason for high MDA concentration in chronic stroke is associated with risk factors and/or atherosclerosis itself; although the concentration of oxidative stress is lower than acute stroke (due to the antioxidant effect and disease course) [41, 44]. Elevation peroxidation results are associated with red blood cell aggregation, and also initiate NADPH-oxidase complex in phagocytes and activate stages of events leading to elevated uptake of low-density lipoprotein by macrophages, and finally leading to the generation of foam cells. By these mechanisms, lipid peroxides are associated with the pathophysiology of atherosclerosis [41].

Six studies focused on the importance of MDA and 8-OHdG in predicting ischemic stroke outcome [9, 12, 18, 38, 39, 42]. Lipid peroxidation due to misfolding of a-synuclein had a pivotal role in neuronal cell death. ROS due to lipid peroxidation could trigger p53 signaling cascade; impaired cell membrane (the damage of ion transport proteins and regulatory systems), induced functional damage of mitochondrial and DNA, and inhibited nucleotide excision repair system [17, 53]. The interaction of MDA and protein and nucleic acid could cause permanent impairment of the enzymes, receptors, and membrane transfer mechanisms [9, 14]. There was an abundant production of MDA and 8-OHdG through ischemia in the penumbral tissue which had minimal oxygen supply (secondary enlargement of brain impairment after focal cerebral ischemia). In the first phase of ischemic stroke, there was an increase of MDA and 8-OHdG because of the failure of defense mechanisms of oxidative stress, that considered from the volume of tissue damage, stroke severity, and outcome [12, 17, 18]. Three studies explained about the role of MDA and 8-OHdG as mortality biomarker in ischemic stroke [33–35]. Lorente et al. reported that MDA level (> 2.27 nmol/mL) and 8-OHdG level (> 4.82 ng/mL) were associated with 30-day mortality of IS patients [33, 35].

Three studies reported about the importance of MDA and 8-OHdG in detecting post-stroke depression (PSD) [10, 11, 17]. Liu et al. (2018) reported that 8-OHdG level above 200 ng/L was positively correlated with PSD [11]. PSD was the most frequent neuropsychiatric disorder after stroke (the prevalence was 29–35%) and was associated with worse functional outcome [53]. Oxidative stress could induce the dysregulation of hypothalamus–pituitary–adrenal axis, affected into the stress control; and the other factors such as age, lifestyle, alcohol, and smoking also contribute in the PSD [10, 11]. Oxidative stress changed the chemical structure of endogenous fatty acids, and produced immunogenic neoepitopes that could induce secondary immune responses, activates indolamine 2,3-dioxygenase and tryptophan catabolites that decreased serotonin level; thus link to depression [53]. Liu et al. (2017) reported about the association of MDA and 8-OHdG and post-stroke cognitive impairment (PSCI); and concluded that MDA (> 2.59 nmol/mL) and 8-OHdG (> 158.63 ng/L) level were associated with PSCI. Vascular inflammation, neurodegeneration, and BBB disruption (extravasation of oxidative stress products) were the main pathophysiology of this association due to hypoxia–ischemia brain cell. Additionally, oxidative stress could promote impairment of peroxisome proliferator-activated receptor (PPAR-γ), a condition that was correlated with vascular aging, neuroinflammation, cerebrovascular white matter lesion, and cognitive impairment [17]. Mueangson et al. (2020) reported about the use of MDA as low hand grip strength (HGS) biomarker in stroke patients. HGS was known as reliable parameter in muscle strength measurement after stroke. The elevation of lipid peroxide and MDA levels were associated with the production by peripheral cells, extracellular generation of hydrogen peroxide by paretic muscles during denervation and associated comorbidities (diabetes, hypertension, and dyslipidemia) [45].

Strength and limitation of the study

This systematic review consisted of 30 studies that discussed the relationship of MDA/8-OHdG and ischemic stroke. The majority of the studies discussed oxidative stress biomarker of acute ischemic stroke.

The limitation of the study was all of the studies were observational, the baseline characteristics were various, the variance of the demography in the human study, confounding variables in each study (human study), sample size, and limited follow-up time.

Future implication

The current systematic review can be a scientific publication to physicians, researchers, and all of the readers associated with the relationship of MDA/8-OHdG and ischemic stroke. Further research is needed with the larger sample size with diverse demographic variances and longer follow-up time, the comparison of these biomarkers with gold standard examination (such as neuroimaging), and also the role of these biomarkers in ischemic stroke treatment.

Conclusion

MDA has the role as oxidative stress biomarker, outcome predictor, mortality predictor, post-stroke cognitive impairment predictor, post-stroke depression predictor, and hand grip strength predictor of ischemic stroke; while 8-OHdG has the role as oxidative stress biomarker, outcome predictor, mortality predictor, post-stroke cognitive impairment predictor, post-stroke depression predictor of ischemic stroke.

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