

Damage-Associated Molecular Patterns and Neuronal Damage Biomarkers in Depression: Systematic Review and Meta Analysis

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Abstract

Results

ts and non-		Depressed Patients			C	Controls			Std. Mean Difference	Std. Mean
	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Rando
	1.1.1 Plasma S100b Level									
	Arolt et al,. 2003	0.0956	0.065	25	0.0486	0.024	25	5.3%	0.94 [0.36, 1.53]	
IRESE and	Arora et al., 2019	0.09696	0.0227	42	0.04721	0.0084	42	5.2%	2.88 [2.26, 3.50]	
IDLOL, and	Fang et al., 2016	0.02101	0.00769	32	0.0168	0.00499	32	5.6%	0.64 [0.14, 1.14]	
lase AND	Hetzel et al., 2005	0.051	0.02	9	0.034	0.01	9	4.1%	1.02 [0.03, 2.02]	
	Jang et al., 2008	0.0641	0.0204	59	0.0696	0.0164	35	5.8%	-0.29 [-0.71, 0.13]	
nal studies	Lei et al., 2023	0.44196	0.12392	37	0.42767	0.12432	61	5.8%	0.11 [-0.29, 0.52]	_
mai studics,	Rothermundt et al., 2001	0.091	0.063	28	0.04	0.023	28	5.4%	1.06 [0.50, 1.62]	
nd with no	Subtotal (95% CI)			232			232	37.1%	0.89 [0.15, 1.63]	
iu with no	Heterogeneity: Tau ² = 0.91; C	hi² = 79.26, df	= 6 (P < 0.000	001); I² =	= 92%					
s assess the	Test for overall effect: Z = 2.3	5 (P = 0.02)								
. (1 1 . (1.1.2 Serum S100b Level									
of level of	Bilginer et al., 2021	1.13701	0.39948	37	0.72867	0.32749	37	5.6%	1.11 [0.62, 1.60]	
· · · · · · · · · · · · · · · · · · ·	Gules et al,. 2020	0.06761	0.01146	10	0.05239	0.0093	10	4.0%	1.40 [0.40, 2.40]	
ger version	Katsanou et al,. 2018	0.00000667	0.0000102	22	0.00000517	0.00000701	30	5.4%	0.17 [-0.38, 0.73]	
-	Levchuk et al., 2023	0.02549	0.01502	21	0.03388	0.00981	25	5.3%	-0.66 [-1.26, -0.07]	
	Polyakova et al., 2015	0.088	0.043	27	0.086	0.011	82	5.7%	0.09 [-0.35, 0.52]	
	Rajewska-Rager et al,. 2021	0.1346	0.1472	52	0.1519	0.1729	31	5.7%	-0.11 [-0.55, 0.34]	
e in S100b	Schroeter et al., 2008	0.0783	0.0525	10	0.0184	0.0235	10	4.0%	1.41 [0.41, 2.41]	
	Tsai and Huang, 2016	0.01667	0.0126	21	0.01567	0.0151	40	5.5%	0.07 [-0.46, 0.60]	
nce (SMD).	Zhao et al,. 2015	25.03	8.24	42	22.4	6.84	42	5.7%	0.34 [-0.09, 0.78]	
	Subtotal (95% CI)			242			307	47.1%	0.34 [-0.04, 0.73]	

Aim: We aimed to assess the comparison of these three markers between depressed patient depressed controls.

Methods: We conducted literature search on 3 electronical databases including PubMed, EM Web of Science using keyword "S100b AND Depression" and "neuron specific eno Depression" and "HMGB1 AND Depression". We included comparative studies, cross section and case control studies. We excluded studies with irrelevant outcomes and subjects, ar available full text. 20 eligible studies assessed the level of S100b marker, 6 eligible studies level of NSE, and 3 eligible studies assessed the level of HMGB1. We retrieved data biomarkers in mean±standard deviation (SD) between two groups. We utilized Review Manag 5.4.1 software to analyze data.

Results: Findings suggested that our analysis of 20 studies revealed a significant increase levels among depressed patients compared to healthy controls. (Standardized Mean Differen 0.55, Confidence Interval: 0.22-0.89, p=0.001). NSE levels showed no statistically significant difference between the groups across 6 studies (SMD: 0.39, CI: -0.32-1.10; p=0.26). Moreover, HMGB1 levels were also statistically significant difference between the groups in all 3 studies examining this marker (SMD: 1.77, CI: -1.31-4.86; p=0.26). It is important to note that the studies exhibited substantial variation ($I^2 \ge 75\%$), suggesting a need for subgroup interpretation.



Difference

Conclusion: This study highlights S100b a potential biomarker for MDD progression. Future research could explore its use in monitoring treatment effectiveness.

Introduction



Emerging evidence that suggests neuroinflammation and alterations in neuronal and glial cell function play crucial roles in the development and progression of MDD.¹ MDD induces pathophysiology changes in the brain. Microglia, the innate immune cells residing in the central nervous system been demonstrated to (CNS), have inflammatory prominently generate cytokines to uphold the neurobiological homeostasis.²



Figure 3. Comparison of S100b level in depressed group and healthy control

Results of meta-analysis show that Increased level of s100b found in depressed persons than healthy control over 20 included studies. Subgroup analysis shows that plasma s100b level is significantly higher compared with serum and CSF s100b level.

	Depres	sed Patient	S	С	ontrols			Std. Mean Difference			Std. Mean	Differen	се	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 99% CI			IV, Rando	<u>m, 99%</u>	CI	
1.1.1 Serum HMGB1 Lev	/el						_							
Shan et al., 2022	11.2	0.67	94	6.1	1.3	230	33.4%	4.41 [3.86, 4.96]					-	
Suleyman et al., 2015 Subtotal (95% CI)	69	33.7	30 124	33.3	14.9	30 260	33.2% 66.6%	1.35 [0.61, 2.09] 2.89 [-0.11, 5.88]			-			
Heterogeneity: Tau ² = 4.6 Test for overall effect: Z =	61; Chi² = 72 1.89 (P = 0	2.82, df = 1 0.06)	(P < 0.0	0001); l² =	99%									
1.1.2 Plasma HMGB1 Le	vel													
Min et al., 2023 Subtotal (95% Cl)	0.117995	0.028077	113 113	0.130194	0.026379	41 41	33.4% 33.4%	-0.44 [-0.91, 0.03] -0.44 [-0.80, -0.08]			•			
Heterogeneity: Not applic Test for overall effect: Z =	able : 2.39 (P = 0	0.02)												
Total (95% CI)			237			301	100.0%	1.77 [-1.31, 4.86]						
Heterogeneity: Tau ² = 7.3 Test for overall effect: Z = Test for subgroup differen	89; Chi² = 29 : 1.13 (P = 0 nces: Chi² =	97.44, df = 2 0.26) 4.67, df = 1	P < 0.	00001); l² = 03), l² = 78	= 99% .6%				-10	-5	(Controls) Depress	5 sed Patien	10 its

Figure 1. Potential Pathway of Modulation of ω -3 PUFAs on S100 β , HMGB1, and NSE in Depression-induced Inflammation

Damage-associated molecular patterns (DAMPs) released from damaged or stressed cells, like HMGB1 and S100 proteins act as danger signals that activate immune cells that leading to inflammatory responses.³ Moreover, following chronic inflammation, the presence of elevated NSE levels can serve as an indicator of neuronal damage or injury.⁴

Methodology



Figure 4. Comparison of HMGB1 level in depressed group and healthy control

Results of meta-analysis show that level of HMGB1 found not significantly higher in depressed persons than healthy control over 3 included studies. Moreover, high heterogenity is presented with >75%.

	Depres	ssed Patie	nts	C	ontrols		ç	Std. Mean Difference	e Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% C	CI IV, Random, 95% CI
1.1.1 Serum NSE Leve	I						_		
Gules et al,. 2020	0.07541	0.03445	10	0.0181	0.01639	10	13.2%	2.03 [0.91, 3.16]	6]
Kozak et al., 2019	4.47	2.71	17	6.19	6.29	36	17.5%	-0.31 [-0.89, 0.27]	7]
Polyakova et al., 2015	11.8	2.6	27	11.9	2.1	82	18.4%	-0.04 [-0.48, 0.39]	9]
Schroeter et al., 2008	7.41	2.18	10	5.91	2.24	10	15.0%	0.65 [-0.25, 1.55]	5]
Wiener et al., 2013 Subtotal (95% Cl)	2.19	1.78	36 100	3.55	2.19	36 174	18.2% 82.2%	-0.67 [-1.15, -0.20] 0.19 [-0.48, 0.86]	
Test for overall effect: Z 1.1.2 CSF NSE Level	.45; Chi² = = 0.54 (P :	22.65, df = = 0.59)	= 4 (P = ().0001);	12 = 82%				
Schmidt et al., 2015 Subtotal (95% Cl)	12.19	5.3	31 31	6.43	4.1	32 32	17.8% 17.8%	1.20 [0.66, 1.74] 1.20 [0.66, 1.74]	
Heterogeneity: Not appl Test for overall effect: Z	icable = 4.37 (P ·	< 0.0001)							
Total (95% CI)			131			206	100.0%	0.39 [-0.32, 1.10]	
Heterogeneity: Tau ² = 0.66; Chi ² = 41.33, df = 5 (P < 0.00001); l ² = 88% Test for overall effect: Z = 1.09 (P = 0.28) Test for subgroup differences: Chi ² = 5.38, df = 1 (P = 0.02), l ² = 81.4%									-4 -2 0 2 Controls Depressed Patients

Figure 5. Comparison of NSE level in depressed group and healthy control

Results of meta-analysis show that level of NSE found not significantly higher in depressed persons than healthy control over 6 included studies. Subgroup analysis shows that CSF NSE level found to be significantly higher in depressed group. Moreover, high heterogenity is presented as >75%.



Inclu				
	1904	Participants	7	
	26	Included articles		
	S100b	HMGB1	NSE	S100b & NSE
	17	3	2	4

Figure 2. Potential Pathway of Modulation of ω-3 PUFAs on S100β, HMGB1, and NSE in Depression-induced Inflammation

Up to September 5th, 2024, we conducted data search on 3 electronic databases, including PubMed, Web of Science, and Embase. The inclusion criteria for inclusion were as follows: (1) Studies that compared relevant biomarkers between depressed patients and non-depressed patients; (2) Studies that included a comparison with a healthy control group; and (3) Studies that reported data on biomarkers, specifically mean values and standard deviations for each group. By adhering to these criteria, we ensured that the selected studies provided robust and comparable data, enabling a comprehensive analysis of the biomarkers' roles in depression as presented in Figure 2.

0 Subgroups Plasma S100b Level Serum S100b Level CSF S100b Level CSF NSE Leve Serum NSE Level 🔷 Plasma HMGB1 Leve Serum HMGB1 Leve

Figure 6. Funnel Plots of Publication bias of (a) S100b (b)HMGB1 (c) NSE

Funnel plots of three analyses present asymmetric distribution that reflect potential publication bias.

Conclusion

This meta-analysis highlights S100b as potential biomarker for MDD progression. Future research could explore their use in monitoring treatment effectiveness for MDD.

References	3. Serna-Rodríguez, M.F.; Bernal-Vega, S.; de la Barquera, J.A.OS.; Camacho-Morales, A.; Pérez-Maya, A.A. The role of damage associated molecular pattern molecules (DAMPs) and permeability of the blood-brain barrier in depression and neuroinflammation. <i>Journal of Neuroimmunology</i> 2022 , <i>371</i> , 577951,
	doi: <u>https://doi.org/10.1016/j.jneuroim.2022.577951</u> .
1. Brites, D.; Fernandes, A. Neuroinflammation and Depression: Microglia Activation, Extracellular Microvesicles and microRNA Dysregulation. Front Cell Neurosci 2015, 9,	4. Pleines, U.E.; Morganti-Kossmann, M.C.; Rancan, M.; Joller, H.; Trentz, O.; Kossmann, T. S-100β Reflects the Extent of Injury and Outcome, Whereas Neuronal
476, doi:10.3389/fncel.2015.00476.	Specific Enolase Is a Better Indicator of Neuroinflammation in Patients With Severe Traumatic Brain Injury. Journal of Neurotrauma 2001, 18, 491-498,
2. Deng, Sl.; Chen, Jg.; Wang, F. Microglia: A Central Player in Depression. Current Medical Science 2020, 40, 391-400, doi:10.1007/s11596-020-2193-1.	doi:10.1089/089771501300227297.