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Matrix metallopeptidase 9 and outcome prediction in patients with acute coronary syndrome

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The aim of this review was to analyse the scientific literature data on matrix metallopeptidase 9 and to analyse the available information on its prognostic value as a marker of negative outcome in the short- and long-term prognosis in patients with acute coronary syndrome.

Materials and methods. In our study was used a recursive literature search strategy at PubMed. The following criteria for inclusion in the analysis were defined – a prospective study in patients with acute coronary syndrome that had data on the effect of MMP-9 levels on short-term and/or long-term outcomes, including mortality and major adverse cardiovascular events. Review articles, clinical cases, animal studies, and studies with insignificant statistical data were not included in the analysis. The depth of the initial search was set at 15 years with a search for similar articles in citations. We selected 5 studies for meta-analysis. Meta-Essentials 1.5 was used for the analysis. Odds ratio and 95 % confidence interval were calculated using the Haenszel method. The association between MMP-9 levels and short-term and long-term outcomes (mortality and major adverse CV events) was determined. The statistically significant level was defined as $P < 0.05$.

Results. The analysis showed no significant association between the level of MMP-9 and the outcome (OR = 1.39; 95 % CI = 0.25–7.79; P = 0.595; I2 = 78 %).

Conclusions. Matrix metallopeptidase 9 is a promising marker for further investigation of its predictive strength of outcome. Despite the opposite results of single studies and no significant association of MMP-9 with outcome further research on this issue is a promising direction.

Ключові слова: гострий коронарний синдром, ММП-9, результат, інфаркт міокарда з підйомом сегмента ST.

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Матрична металопептидаза 9 і прогнозування результатів у пацієнтів із гострим коронарним синдромом

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Мета роботи – аналіз відомостей наукової літератури про матричну металопептидазу 9 (ММП-9) та інформації про її прогностичну цінність як маркера негативного результату в короткостроковому та віддаленому прогнозі в пацієнтів із гострим коронарним синдромом.

Матеріали та методи. Використали рекурсивну стратегію пошуку відомостей у фаховій літературі в PubMed. В аналіз включали проспективні дослідження за участю пацієнтів із гострим коронарним синдромом, де були відомості про вплив рівня ММП-9 на короткостроковий та/або віддалений результат, включаючи смертність і провідні несприятливі серцево-судинні події. Оглядові статті, клінічні випадки, дослідження на тваринах і роботи з незначущими статистичними даними в аналіз не залучали. Глибина первинного пошуку – на рівні 15 років із пошуком схожих статей із цитування. Для метааналізу обрали 5 досліджень. Під час аналізу використовували програму Meta-Essentials 1.5. Відношення шансів і 95 % довірчий інтервал розраховували методом Хаенсцеля. Визначали асоціацію між рівнем ММП-9 і короткостроковими, віддаленими наслідками (смертність і головні несприятливі серцево-судинні події). Статистично значущий рівень – $p < 0,05$.

Результати. Аналіз не виявив вірогідного зв'язку між рівнем ММП-9 і результатом (OR = 1,39; 95 % CI = 0,25–7,79; p = 0,595; I2 = 78 %).

Висновки. Матрична металопептидаза 9 – перспективний маркер для продовження вивчення його прогностичної сили щодо прогнозу результату. Незважаючи на протилежні результати поодиноких досліджень і відсутність значущого зв'язку ММП-9 і результату, перспективними є наступні дослідження в цьому напрямі.

Matrix metallopeptidase 9 (MMP-9) review. Coronary artery disease (CAD) is a disease depending on several factors and characterized by a high mortality rate all over the world. The main cause of CAD is atherosclerosis that is following by plaque formation in the endothelium of arteries [1]. In cardiovascular diseases, alterations in the breakdown and regeneration of the extracellular matrix (ECM) take place due to instability of the arterial wall secondary to the injury seen in this type of disease [2].

ECM plays a very important supporting role for organs and tissues, it also participates in controlling the cell cycle and cell motility, surveillance of cells, and its apoptosis, as well as the dealing out growth factors, acts as a local store for them, capable to integrate multiple signals into cells. The extracellular matrix regulates a cell's dynamic behavior. The ECM is made up of proteoglycans; glycosaminoglycans; structural proteins, such as collagen and elastin; cell adhesion molecules, such as fibronectin and laminin,

integrins, cadherins; and proteases called matrix metalloproteases (MMPs) [3,4]. Matrix metalloproteinase (MMP) is a proteolytic enzyme that has been identified in normal tissues as well as it has been expressed in human disease. Myocardium is one of the sites of MMP expression and is likely to contribute to ECM changes and myocardial remodelling, vascular atherosclerotic plaques instability and its future rupture. MMPs are a family of protease enzymes. At present, the MMP family itself includes 28 members [5].

Based on their sub-cellular distribution and specificity for components of the ECM, the MMPs are divided into membrane-type matrix metalloproteases (MT-MMPs), collagenases, gelatinases, stromelysins, and matrilysins. Collagenases (MMP-1, MMP-8, MMP-13, and MMP-18) degrade triple-helical fibrillar collagen, which is fundamental in bone and ligaments. Gelatinases (MMP-2 and MMP-9) are involved in different cellular process including angiogenesis and neurogenesis; these proteases alter the molecules of the basal lamina, subsequently leading to cell death. Stromelysins (MMP-3, MMP-10, and MMP-11) are small proteases that degrade segments of the ECM. Matrilysins (MMP-7 and MMP-26) process cell surface molecules and digest ECM components. MT-MMPs have collagenolytic activity and may activate some proteases and components of the cell surface [3,4,6].

All MMPs share the following functional features [7]: they degrade the ECM component; almost all of them are secreted in a latent proform and need to be activated for their proteolytic activity; they contain zinc at their active site; they require calcium for their stability; they function at neutral pH; and they are inhibited by specific tissue inhibitors of metalloproteinases (TIMPs). They are expressed at low level in normal adult tissue turnovers such as reproduction, development, tissue repair, or immune response and are upregulated during pathological processes including inflammation, autoimmune diseases, neurogenerative disorders, tumor invasion and metastasis, and heart injury [8]. One of the MMP family member, MMP-9, also known gelatinase B, bearing the ability to degrade type IV collagen and elastin, the principal components in the arterial vessel wall, is primarily an inducible enzyme and is involved in inflammatory process, is a widely investigated member of the MMP family [9]. In addition, MMP-9 has an O-glycosylated domain and three fibronectin repeats (MMP-2 also has fibronectin repeats). These structural domains form an inactive 92 kDa pro-MMP-9 or an active 82 kDa MMP-9. MMP-9 also exists in a third form as a 65 kDa protein that lacks the carboxyterminal hemopexin domain and amino terminal propeptide [10–12].

Abnormalities of MMPs production and activity have been shown to be involved in several vascular diseases in many previous studies [9]. In the past few decades, growing evidence from basic and clinical studies have demonstrated the important role of MMPs in the progression of left ventricular dimension, remodelling and mortality following AMI [13]. MMP-9, has been shown to involve in the pathogenesis of cardiovascular diseases. Furthermore, MMP-9 SNP rs3918242 and circulating MMP-9 level are associated with CAD progression and myocardial infarction, arterial wall stiffness and high mortality in patients with CAD, while the mechanisms are not completely clear [14].

MMP-9 in patients with acute coronary syndrome (ACS). MMP-9 is involved in the immune response and is important in vascular inflammation and the development of atherosclerosis and acute coronary syndrome [15–19]. As authors say, during stress endothelial cells expose an increase in MMP-9 expression and activity. Afterwards, it contributes the degradation of extracellular matrix what could intensify an infiltration of inflammatory cell. As shown histopathological studies, MMP-9 was primarily spread in the regions of carotid atherosclerotic plaques [20] which includes inflammatory cells [21,22].

It was described that MMP-9, despite of infiltration of monocyte/macrophages inside lesions, does not affect the fatty streak size [23]. MMP-9 participate in a promotion in the vascular smooth muscle cells (VSMCs) migration. As known, VSMCs can produce vascular endothelial growth factor (VEGF), which takes a crucial part in neovascularization [22,24].

Others reported that MMP-9 play an important role in protection of plaque in instability due to an enlargement of collagen deposit after overexpression of pro-MMP-9 in macrophages [25]. Also, as a result of the loss of MMP-9 smooth muscle cells (SMC) volume decreases, area of plaque and macrophage infiltration growth [26].

Early increasing of MMP-9 level is associated with the extensiveness of left ventricular remodeling and circulating leukocytes levels [27]. Another study has shown increased serum levels of MMP-9 in patients with coronary artery disease (CAD) and proposed that CAD could conduct to 1562CG transformation of MMP-9 gene into genetic polymorphism, in consequence it contributes to remodeling of arteries and expanding unstable atherosclerotic plaques [28]. Additionally, deprivation of MMP-9 can avoid aortic dilatation and abdominal aortic aneurysms formation [29]. The loss of MMP-9 can also decrease levels of C-reactive protein in atherosclerotic plaques of aorta, pointing out that shortage of MMP-9 can influence on stabilization of plaques due to suppression of their inflammation [30]. Montero et al. suggested that local and systemic CRP-associated MMP activation can be a link between inflammation and plaque vulnerability [31]. Gough et al. showed that expression of MMP-9 in macrophages in vitro significantly enhances elastin degradation and causes significant destruction of plaques when overexpressed by macrophages in apoE-/-mice in vivo [32].

Aim

The aim of this review was to analyze the scientific literature data on matrix metallopeptidase 9 and to analyse the available information on its prognostic value as a marker of negative outcome in the short- and long-term prognosis in patients with acute coronary syndrome.

Materials and methods

We carried out a comprehensive systematic literature search in PubMed for Relevant Research using the following keywords “Matrix metalloproteinase 9”,

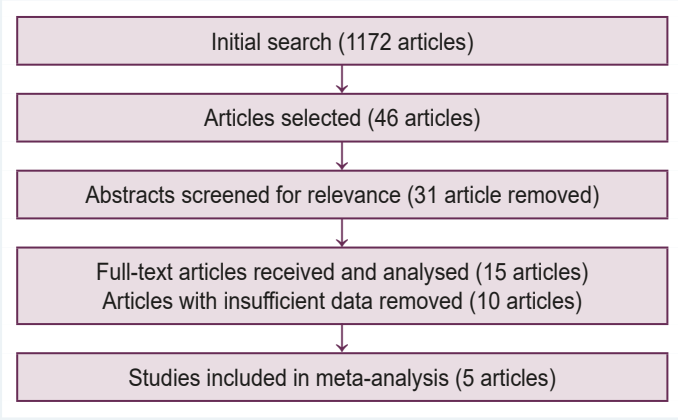
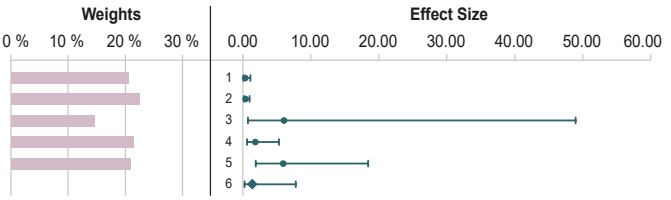


Fig. 1. Article analysis process.

Table 1. Study characteristics

Study Name	Study design	Country	Age	MMP-9 cut-off	Cohort	Follow-up period
Zhu J. J. et al. [33]	prospective study	China	60	398.2 ng/ml	155	14 days
Somuncu M. U. et al. [34]	prospective study	Turkey	56	12.92 ng/ml	204	2 years
Wang K. F. et al. [35]	prospective study	Taiwan	63	1.1 ng/ml	96	43 ± 12 months
Kobayashi N. et al. [36]	prospective study	Japan	65	65.5 ng/ml	249	2 years
Apple F. S. et al. [37]	prospective study	US	57	233.7 ng/ml	457	4 months

Table 2. Forest plot of the relationship between MMP-9 level and outcome in patients with ACS



No.	Study name	Odds Ratio	CI Lower limit	CI Upper limit	Weight
1	Somuncu M. U. et al. (2020)	0.34	0.10	1.11	20.63 %
2	Wang K. F. et al. (2013)	0.39	0.16	0.99	22.42 %
3	Kobayashi N. et al. (2016)	6.04	0.75	48.96	14.59 %
4	Apple F. S. et al. (2007)	1.82	0.62	5.31	21.38 %
5	Zhu J. J. et al. (2017)	5.92	1.90	18.43	20.98 %

Combined Effect Size	
Odds Ratio	1.39
CI Lower limit	0.25
CI Upper limit	7.79
PI Lower limit	0.03
Z-value	0.53
One-tailed P-value	0.297
Two-tailed P-value	0.595
Number of incl. subjects	1161
Number of incl. studies	5

"MMP-9", "ACS", "acute coronary syndrome", "STEMI", and "Outcome". Any country or language restriction was in our search. Moreover, we used manual searching of references for complementary relevant articles.

The following criteria for inclusion in the analysis were defined – a prospective study in patients with ACS that had data on the effect of MMP-9 levels on short-term and/or long-term outcomes, including mortality and major adverse CV events. Review articles, clinical cases, animal studies, and studies with insignificant statistical data were not included in the analysis (*Table 3*).

This meta-analysis was performed using Meta-Essentials 1.5 (Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License).

Odds ratio and 95 % confidence interval were calculated using the Haenszel method. The association between MMP-9 levels and short-term and long-term outcomes (mortality and major adverse CV events) was determined. The statistically significant level was defined as $P < 0.05$.

Results

After a systematic analysis of 1172 articles, 46 articles were selected for further analysis, of which 15 articles were selected for detailed study. Of these, 10 articles were excluded due to the impossibility of using the data for further analysis. 5 articles were selected for meta-analysis (*Fig. 1*).

Our meta-analysis included 5 cohorts with a total number of 1161 patients with ACS. The studies were carried out between 2007 and 2020. All the studies were prospective and were carried out in different countries. Due to the lack of generally accepted referral values of the MMP-9 level, cut-off points vary from 1.1 ng/ml to 398.2 ng/ml. All selected studies are presented in *Table 1*.

Association between High MMP-9 level and poor outcome in patients with ACS. The analysis showed no significant association between the level of MMP-9 and the outcome (OR = 1.39; 95 % CI = 0.25–7.79; P = 0.595; I2 = 78 %) (*Table 2*).

Publication bias. The funnel plot of the association of MMP-9 poor outcome in patients with ACS symmetrical on inspection, suggesting low risk of publication bias (*Fig. 2*).

Excluded studies with sufficient data. *Table 3* provides systematic information on studies that could not be included in our meta-analysis due to the lack of accurate data or an incompatible type of analysis.

Discussion

As we know, MMP-9 has shown some effectiveness as an ACS marker alone [38,49,50] and as part of multimarket discriminative model [51]. As for short- and long-term prognosis, however, research data diverge and show both positive and negative results, which may indicate the impact of other factors that may have been overlooked. As shown by A. Dominguez-Rodriguez, the level of MMP-9 in patients with diabetes mellitus was significantly higher than in patients with ACS alone. As we know, the development of T2DM leads to the activation of systemic inflammation and vascular damage, which is

Table 3. Excluded significant studies

Study name	Study design	Cohort	Follow-up period	Outcome
Lahdentausta L. et al. [38]	prospective study	343	6 years	Authors observed 343 post-ACS patient for 6 years. MMP-9 was a significant predictor of fatal events (HR 2.88 (1.32–6.27), P = 0.025, Q4 vs. Q1) but not non-fatal events and MACE (HR 4.15 (1.87–9.23), P = 0.006).
Opstad T. B. et al. [39]	prospective study	243	1 year	Authors observed a non-significant MMP-9 level increase in patient with events during their 1-year follow-up period.
El-Aziz T. A. A. et al. [40]	prospective study	184	6 months	MMP-9 was an independent risk factor for mortality but not morbidity during 6 months follow-up
Hamed G. M. and Fattah M. F. A. [41]	prospective study	120	6 months	Authors conducted a 6-month follow-up of 120 subjects, of whom 75 had ACS. After performing ROC analysis, they determined the best cut-off level of MMP-9 for the outcome prediction at 4700 pg/ml.
Tan J. et al. [42,43]	prospective study	228	3 years	Logistic regression did not show MMP-9 as an independent predictor of mortality.
Dhillon O. S. et al. [44]	prospective study	1024	134–1059 days	Authors observed 1024 patients with AMI for an average of 519 days. The Cox analysis carried out by the authors did not show a significant relationship between the level of MMP-9 and all-cause mortality (unvariative – HR 1.02, 95 % CI (0.68–1.51), P = 0.407, multivariative – HR 1.18, 95 % CI (0.76–1.82), P = 0.47).
Brügger-Andersen T. et al. [45]	prospective study	298	18–45 months	Authors observed 298 patients with acute MI. MMP-9 showed no statistical significance in predicting outcome over 45 months (HR 0.78, SD 95 %, CI (0.39−1.53), P = 0.461).
Giansante C. et al. [46]	prospective study	100	4–15 days	Authors observed 40 patients with ACS, 40 patients with CSA and 20 healthy participants for an average of 6 days. ROC analysis showed no statistically significant difference in clinical outcome.
Dominguez-Rodriguez A. et al. [47]	prospective study	120	in-hospital observation	Authors observed 72 patients with STEMI and 48 patients with STEMI and T2DM. Multivariate analysis showed that elevated MMP-9 levels were associated with increased in-hospital mortality (OR 2.10, 95 % CI (1.80–2.60), P = 0.006) and cardiogenic shock (OR 2.30, 95 % CI (1.90–2.80), P < 0.0001). Moreover, MMP-9 levels were significantly higher in patients with STEMI and diabetes.
Jordakieva G. et al. [48]	prospective study	120	30 days	Authors showed that in 30-day period survivors had a significantly lower MMP-9 level than deceased patients (OR 1.67, SD 95 %, CI (1.10–2.53), P = 0.016). Moreover, MMP-9 was independent predictor for 30-day survival in patient with cardiac disease only (P = 0.002).

manifested by the release of pro-inflammatory markers, including MMP-9 [52]. A recent study has shown an increase in the concentration of MMP-2 and MMP-9 in patients with type 1 and type 2 diabetes, especially with the development of renal injury [53]. Moreover, the intake of glucose by healthy volunteers also leads to an increase in the expression of the MMP-2, MMP-9, and TF genes [54]. Peng Z. et al. [55] showed that selective inhibitor MMP-9(R)-ND-336 accelerates wound healing in infected diabetic mice. The effect of renal injury on MMP-9 levels in these studies also cannot be completely ruled out, since an increased level of active MMP-9 and MMP-9/TIMP-1 correlates with a decrease in renal function [56]. These circumstances impose some restrictions on the use of this marker as an independent predictor of patient survival after ACS and require special attention to the study design and also opens new horizons for further study of this marker, not only as a marker for predicting survival and mortality, but also as a potential therapeutic target.

Somuncu M. U. et al. [34] found a relationship for the incidence of no-reflow in patients with high MMP-9 levels. Another study found that the level of MMP-9 in the culprit coronary artery in AMI patients was significantly higher in the no-reflow group than in the reflow group [57]. Kuliczkowski W. et al. [58] also showed that patients with high MMP-9 levels are more likely to experience no-reflow, which is an independent factor in short-term mortality in patients with ACS [59]. There are also known studies proving the relationship between the occurrence of ventricular remodeling and a high level of MMP-9 in patients after ACS [60], which brings us to the potential benefit of determining the level of MMP-9 as a predictor of patient survival.

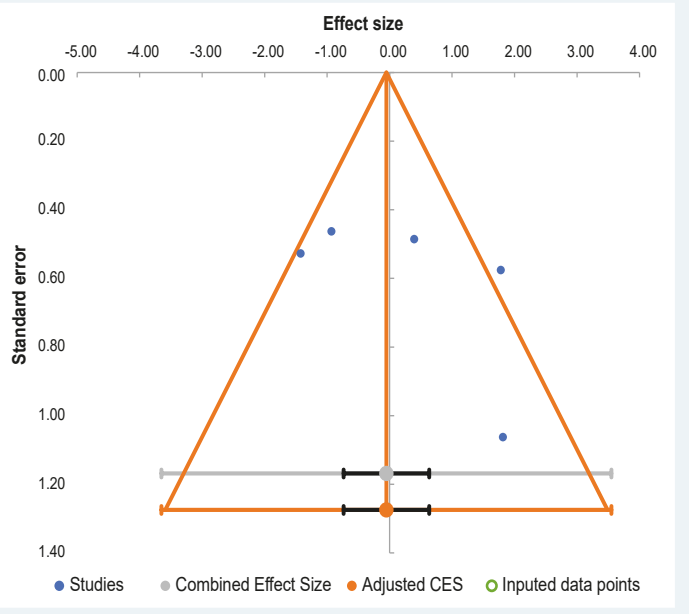


Fig. 2. Funnel plot of the association of MMP-9 poor outcome in patients with ACS.

Also, when analyzing the data of the studies included in this review, it is necessary to note the variety of methods for analyzing the assessment of the prognosis, the duration of observation and the absence of a generally accepted reference value for MMP-9. These circumstances do not allow to fully systematize the data obtained by each author and come to a conclusion regarding the predictive power of the outcome of this biomarker. However, these circumstances pose new

challenges and horizons to overcome in further research on this topic.

Conclusions

MMP-9 is a promising marker for further investigation of its predictive strength of outcome. Despite the opposite results of single studies and no significant association of MMP-9 with outcome further research on this issue is a promising direction.

Study limitations

We encountered some significant limitations in performing this analysis. First, due to the lack of MMP-9 cut-off reference values, the values varied greatly, which leads us to a possible reason for the lack of correlation in the results of the meta-analysis performed. It is necessary to determine the cut-off value in future research.
Secondly, there is an insufficient number of studies on this topic, which would clearly distinguish between long-term and short-term prognosis of cardiac events and mortality.
Thirdly, due to the small number of suitable studies, we could not separate the data by observation time.

Conflicts of interest: authors have no conflict of interest to declare.
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