The role of NLRP3 inflammasome in atherosclerotic disease: Systematic review and meta-analysis

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Background

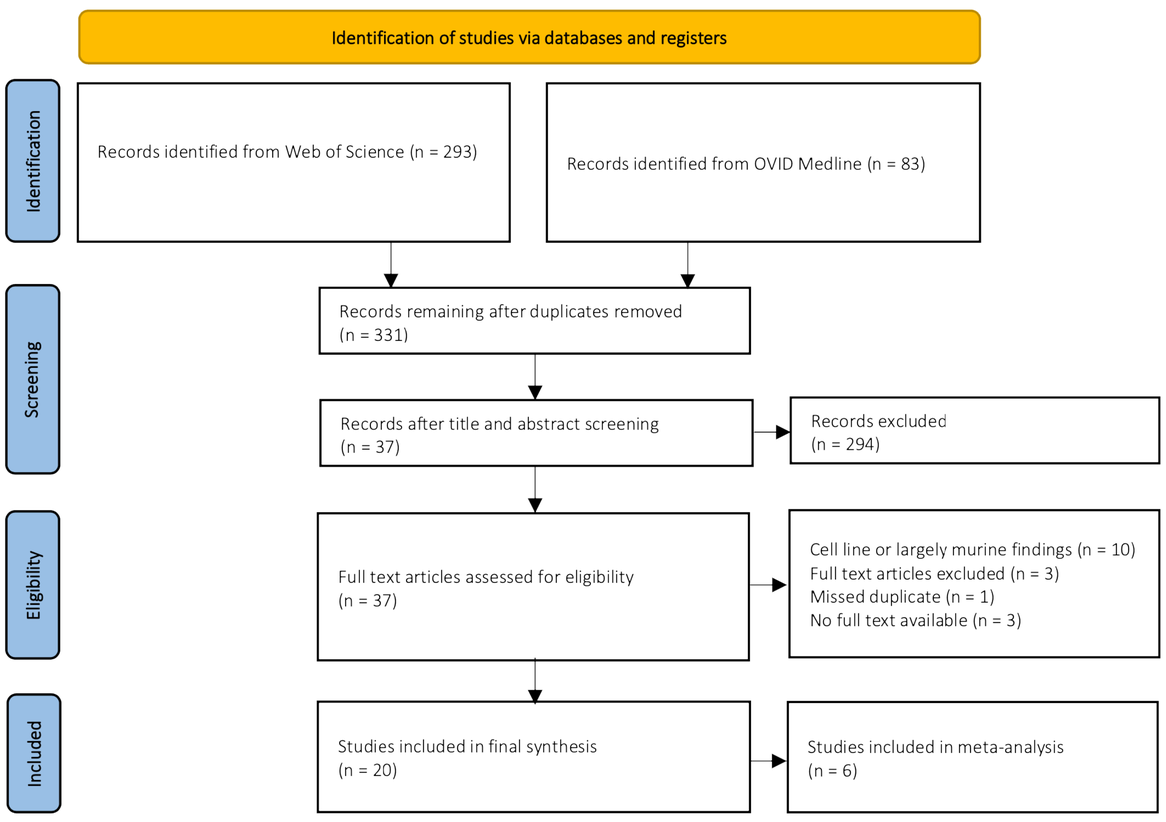
Atherosclerosis is a chronic, progressive cardiovascular disease characterised by cholesterol deposition. Recent literature has suggested NLRP3 (NOD [nucleotide oligomerization domain]-, LRR [leucine-rich repeat]-, and PYD [pyrin domain]- containing protein 3) inflammasome is a key inflammatory mediator in the development, progression, and destabilisation of atherosclerotic plaques. Current literature has been focussed largely on murine findings.

Objective

The aim of this review was to evaluate the current literature on the role of NLRP3 in human atherosclerosis.

Methods

This systematic review was registered on the PROSPERO database (ID = CRD42022340039) and involved the search of a total of 8 databases. Records were screened in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. A total of 20 studies were included and quality assessed using the NIH: NHLBI tool. 6 were eligible for meta-analysis using RevMan 5.4.1.



Results

We identified 20 relevant articles representing 3388 participants. mRNA levels of the protein, NLRP3 and downstream cytokine counterparts, IL-1β and IL-18 were found to be strongly associated with atherosclerotic disease. Fold changes of NLRP3 mRNA levels were most strongly associated with high-risk atherosclerotic disease, compared to controls (0.85 [95% CI: 0.44-1.25]). IL-1β mRNA fold change was more robustly associated with high-risk atherosclerotic disease (0.62 [95% CI: 0.14-1.11]) than IL-18 (0.47 [95% CI: 0.07-0.86]).

Expression of NLRP3 in atherosclerotic disease and related polymorphisms

An emerging body of evidence has suggested a high expression level of the NLRP3 inflammasome in atherosclerotic disease and four included studies have supported such findings.[28,29,33,39] Three of these supported such findings in PBMCs and carotid atherosclerotic plaques, when relative mRNA fold change was compared to controls.[28,33,39] All three studies by Rajamaki, Shi and Zhu et al also partially confirmed such findings with an associated higher protein expression level of NLRP3 inflammasome components such as ASC and caspase-1 as well as down-stream cytokines such as IL-1β and IL-18.[28,33,39] A meta-analysis of eligible studies determined that NLRP3 mRNA levels had a mean difference of 0.84 [95% CI: 0.44-1.25] in high-risk, compared to controls.[21-23,28,31,33] This is seen in Figure 2, indicating that a greater expression of NLRP3 in high- risk atherosclerotic disease versus controls.

Figure 2: Fold change of NLRP3 mRNA levels in controls vs. high-risk atherosclerotic

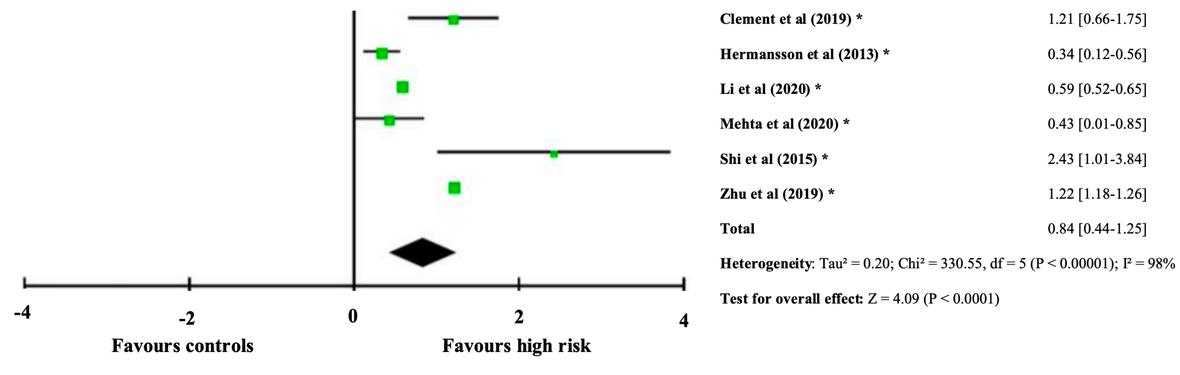


Figure 3 Canonical activation of the NLRP3 inflammasome

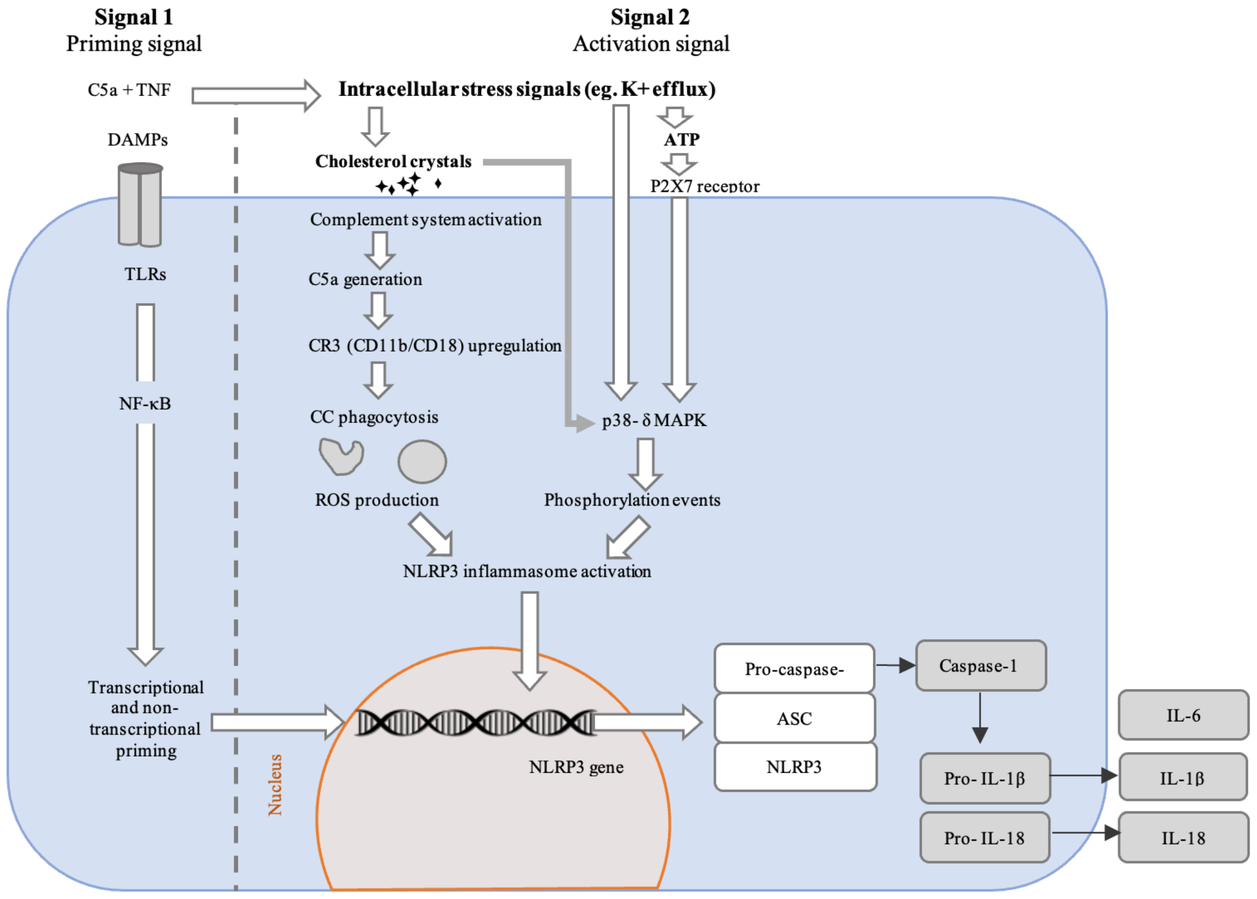


Fig 3: Canonical activation of NLRP3 inflammasome activation.

This diagram summarises the two-step canonical activation of the NLRP3 inflammasome consisting of a priming signal and an activation signal. DAMPs – damage-associated molecular pattern, NF-kB – nuclear factor kappa light-chain-enhancer of activated B cells, C" – complement system, CR3 – complement-receptor 3, CC – cholesterol crystals, ROS – reactive oxygen species, ASC – apoptosis-associated speck-like protein.[23,26,35,39]

Downstream cytokine production from NLRP3

Two studies have linked NLRP3 inflammasome activation with the production of downstream cytokines.[30,34] In a study by Shateri et al., NLRP3 and IL-1β were concurrently increased in the CAD group compared to controls.[30] This remained a notable correlation when gene expression and mRNA levels of NLRP3 and IL-1β was examined and data was adjusted for potential confounders.[30] From the meta-analysis of eligible studies, the mean difference in mRNA fold change of IL-1β was 0.63 [95% CI: 0.14-1.11, p = 0.01] while IL-18 was 0.47 [95% CI: 0.07-0.86, p = 0.02].[22,23,31] This favoured a higher expression of both IL-1β and IL-18 in high-risk atherosclerotic disease compared to controls. This is seen in Figures 4 and 5. In the second study by Afrasyab, NLRP3 inflammasome activation was also linked with IL-18.[34] However, a positive correlation was most strongly associated between NLRP3 and IL-1β.[30] Other studies also reported a correlation between NLRP3 levels and both IL-1β and IL-18 in CAD.[27,28,30]

Figure 4: Fold change of IL-1β mRNA levels in controls vs. high-risk atherosclerotic disease

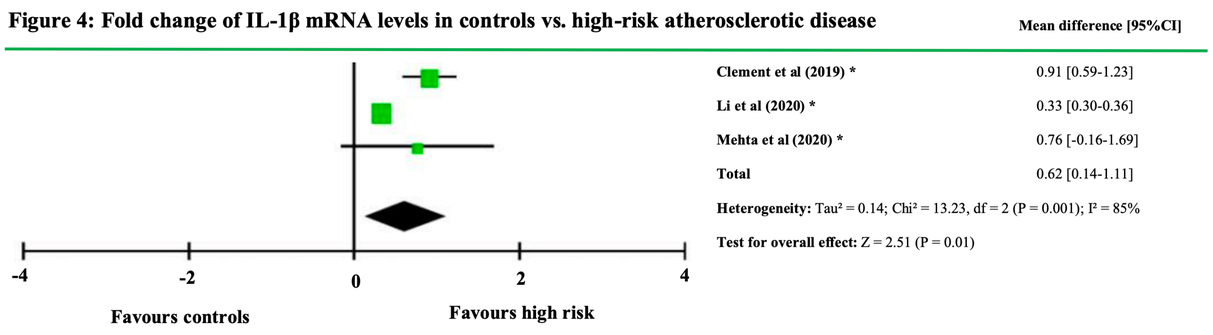
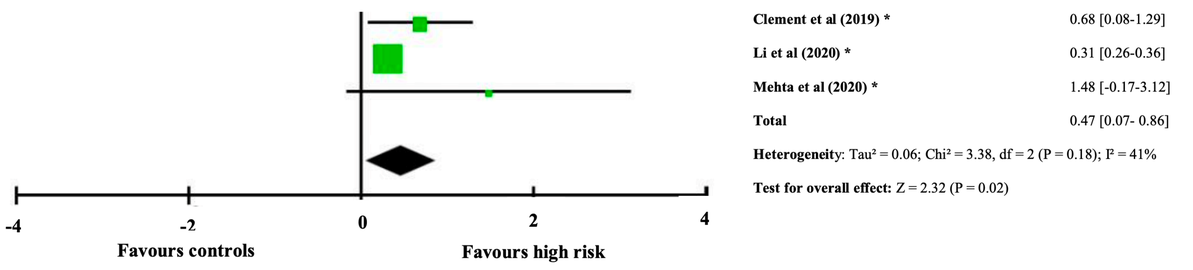


Figure 5: Fold change of IL-18 mRNA levels in controls vs. high-risk atherosclerotic disease



Conclusion

NLRP3, IL-1β, and IL-18 are associated with high-risk atherosclerotic disease. However, given the scope of this review, the role of this inflammasome and its cytokine counterparts in acting as prognosticators of CAD severity is unclear. Several upstream activators such as cholesterol crystals are involved in the canonical or non-canonical activation of the NLRP3 inflammasome and its downstream cytokines. These findings highlight the necessity for further research to delineate the exact mechanisms of NLRP3 inflammasome activation and potential drug targets.