

Role of Autoimmunity and Autoinflammation in the Pathogenesis of Idiopathic Recurrent Pericarditis

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Abstract Idiopathic recurrent pericarditis is the most common and troublesome complication of acute pericarditis affecting about one third of such patients. The pericardium may be involved in different systemic autoimmune diseases (i.e., systemic lupus erythematosus, rheumatoid arthritis, progressive systemic sclerosis, mixed connective tissue disease, Sjogren's Syndrome, polyarteritis, giant cell arteritis, other systemic vasculitides) either in a symptomatic form (usually during the active phase of the disease) or as asymptomatic pericardial effusion. Moreover, idiopathic recurrent pericarditis mimicks hereditary periodic fever

syndromes (HPFSs). HPFSs are a group of disorders characterized by primary dysfunction of the innate immune system mostly caused by mutations of genes involved in the regulation or activation of the inflammatory response, without any apparent involvement of antigen-specific T cells or significant production of autoantibodies. These disorders usually manifest in the pediatric population, with onset ranging from the first hours to the first decade of life, however a limited number of patients experience disease onset during adulthood.

Keywords Recurrent pericarditis · Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) · Familial Mediterranean fever (FMF) · Autoinflammatory disorders

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Introduction

Pericarditis is a common disease which may account for about 5% of presentations to emergency departments for non-ischaemic chest pain [1] and may be caused by a wide spectrum of different conditions. Nevertheless, the etiological search is often inconclusive, and about 85% of cases are classified as idiopathic or are presumed to be viral in developed countries [2–4]. Tuberculosis is the most common cause of pericardial diseases in developing regions of the world [5]. Table 1 shows the most common causes of acute pericarditis.

Recurrent pericarditis represents the most troublesome complication of acute pericarditis, occurring in 30% to 50% of patients with acute pericarditis, and is generally presumed to be an autoimmune process [4].

Following a documented first attack of acute pericarditis according to accepted diagnostic criteria, the diagnosis of idiopathic recurrent acute pericarditis (IRAP) can be made

Table 1 Summary of the main causes of acute pericarditis

Infectious	
Viral	Most common—echovirus and coxsackievirus; usual—influenza, EBV, CMV, adenovirus, varicella, rubella, mumps, HBV, HCV, HIV, parvovirus B19, and human herpes virus 6
Bacterial	Most common—tuberculous, <i>Coxiella burnetii</i> ; other rare bacterial infections may include pneumo-, meningo-, gonococcosis, <i>Haemophilus</i> , staphylococci, chlamydia, mycoplasma, legionella, leptospira, listeria
Parasitic	Very rare—echinococcus, toxoplasma
Fungal	Rare—histoplasma more likely in immunocompetent patients, aspergillosis, blastomycosis, candida more likely in immunosuppressed host
Non infectious	
Autoimmune	Pericardial injury syndromes (post-myocardial infarction syndrome, post-pericardiectomy syndrome, post-traumatic pericarditis) Systemic autoimmune diseases (Sjogren's syndrome, systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, systemic vasculitides) Autoimmune (other presumed to have an autoimmune cause after exclusion of infectious and neoplastic causes)
Autoinflammatory	
Monogenic	TRAPS FMF
Multifactorial	Behçet's Disease Crohn's disease Sarcoidosis
Neoplastic	Primary tumors (rare, above all pericardial mesothelioma) Secondary metastatic tumors (common, above all lung and breast cancer, lymphoma)
Metabolic	Gout, myxedema, uremia
Traumatic	Direct injury (penetrating thoracic injury, esophageal perforation) Indirect injury (non-penetrating thoracic injury, radiation injury)
Drug-related	Procainamide, hydralazine, isoniazid, and phenytoin (lupus-like syndrome), penicillins (hypersensitivity pericarditis with eosinophilia), doxorubicin and daunorubicin (often associated with a cardiomyopathy, may cause a pericardiopathy, as other chemotherapy agents)

CMV cytomegalovirus; *EBV* Epstein–Barr virus; *HBV* hepatitis B virus; *HCV* hepatitis C virus; *HIV* human immunodeficiency virus; *TRAPS* tumor necrosis factor receptor-associated periodic syndrome; *FMF* familial Mediterranean fever

when at least two of the following criteria are present: (1) chest pain, (2) pericardial friction rub, (3) ECG changes (typically widespread ST segment elevation, PR depression), (4) new or worsening pericardial effusion, (5) a clinical diagnosis of acute pericarditis [6].

Additional evidence of active inflammation such as elevated C-reactive protein is a confirmatory finding [4].

Some patients experience only a single recurrence, but in many cases pericardial pain may return unexpectedly at varying intervals during a period that may extend over many years. The number of recurrences and the interval between the episodes vary among patients and are not predictable in individual cases.

Recurrent Pericarditis and “Autoimmunity”

The pericardium may be involved in patients with systemic lupus erythematosus, rheumatoid arthritis, progressive systemic sclerosis, mixed connective tissue disease, Sjogren's Syndrome, polyarteritis, giant cell arteritis, or other systemic vasculitides. Symptomatic pericarditis can occur with all of these disorders, during the active phase of the disease. A systemic autoimmune disease was shown to be responsible for acute pericarditis in 33 of 453 patients (7.3%) [6]. In other cases, the pericardial involvement may be subclinical with a clinically silent pericardial effusion [7].

Antinuclear antibodies (ANA) have been detected in 43.4% patients with IRAP, and in only 9.8% of controls. Low titres (1/40–1/80) have been found in the majority of cases, while a moderate positivity (1/160–1/320) can be detected in 26.7% of cases [8]. These data suggested a potential autoimmune origin of recurrent pericarditis in

about 40% of IRAP patients. However, although ANAs are often used as a screening test, they have been shown to be equally distributed in patients with or without a definite rheumatological diagnosis [8] and, in addition, their serum positivity does not necessarily imply a rheumatological diagnosis, since a combination of symptoms, signs, and laboratory findings is also required.

Recently, the frequency of serum anti-heart (AHA), anti-intercalated-disk (AIDA), and non-cardiac-specific autoantibodies was assessed in 40 IRAP patients [9]. The frequencies of AHA and of AIDA were higher (50%; 25%) in IRAP than in non-inflammatory cardiac disease (NICD) (4%; 4%), ischaemic (1%; 2%), or normal subjects (3%; 0%). AHA and/or AIDA were found in 67.5% patients with IRAP. Of the non-cardiac-specific antibodies, only antinuclear autoantibodies at titre $\geq 1/160$ were more common in IRAP (5%) versus normal (0.5%). In addition, the AIDA in IRAP were associated with a higher number of recurrences and hospitalizations, whereas high-titre AHA were associated with a higher number of recurrences. The detection of AHA and of AIDA strongly supports the involvement of autoimmunity in the majority of patients with IRAP.

Autoimmune responses may develop in predisposed individuals following several exogenous triggers [10]. Autoimmune responses can certainly play a role in the pathogenesis of recurrent post-viral pericarditis, through activation of the innate immune system, in predisposed hosts [2, 11–13].

Bacterial- and viral-derived products called pathogen-associated molecular patterns (PAMPs) may interact with the toll-like receptors (TLRs), molecules that are expressed both at the cell surface of dendritic cells

Fig. 1 Schematic representation of the interaction between innate and adaptive immunity. Presentation of antigen-derived peptides by MHC II molecules on the APC surface leads to T cell activation. APC stimulation by PAMPs and DAMPs through signaling pathways leading to inflammasome and NF- κ B activation induces cytokine expression, which enables primary lymphocyte responses. Abbreviations: *DAMPs* damage-associated molecular patterns; *PAMPs* pathogen-associated molecular patterns; *MHC II* major histocompatibility complex MHC class II

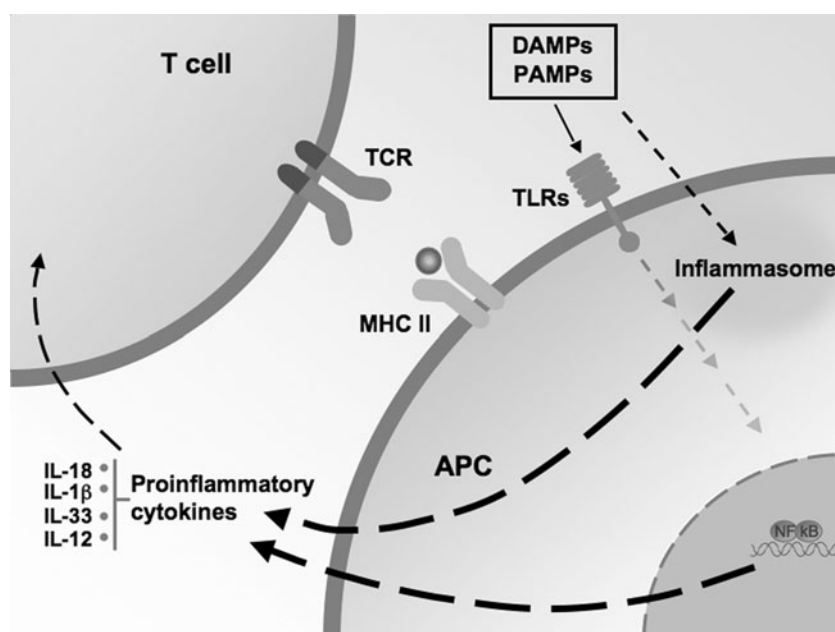


Table 2 The table summarizes the main monogenic autoinflammatory disorders

	Diseases	Clinical features	Gene chromosome	Protein	Transmission
HPFSs	FMF	Fevers, erysipeloid lower limbs erythema, arthralgia, monoarthritis, myalgia, serosal inflammation, and amyloidosis	<i>MEIVF</i> 16p13.3	Pyrin	AR
	HIDS	Fevers, intermittent morbilliform rash, arthralgia, severe abdominal pain, lymphadenopathy	<i>MVK</i> 12q24	Mevalonate kinase	AR
CAPS	TRAPS	Fevers, migratory skin rash, conjunctivitis, periorbital edema, arthralgia, arthritis, serosal inflammation, and amyloidosis	<i>TNFRSF1A</i> 12p13	p55 TNF- α receptor	AD
	FCUS	Fevers, cold-induced urticaria, conjunctivitis, arthralgia	<i>NLRP3</i> 1q44	Cryopyrin	AD
	MWS	Fevers, urticarial rash, conjunctivitis, episcleritis, arthralgia, sensorineural hearing loss, and amyloidosis			
	CINCA	Fevers, urticarial rash, conjunctivitis, episcleritis, uveitis, papilledema, arthralgia, arthropathy (osseous overgrowth), chronic meningitis, sensorineural hearing loss, amyloidosis			
PGA	BS and EOS	Fevers, erythematous or tan scaly rash, panuveitis, granulomatous polyarthritis, camptodactyly	<i>CARD15/NOD2</i> 16q12	CARD15	AD
Pyogenic disorder	PAPA	Cystic acne, pyoderma gangrenosum, and sterile neutrophilic arthritis	<i>PSTPIP1</i> 15q24-q25.1	PSTPIP1	AD
	Majeed's syndrome	Bone pain, osteitis, organomegaly, hypochromic microcytic anemia	<i>LPIN2</i> 18p	LPIN2	AR
	CRMO (murine)		<i>PSTPIP2</i> 18p	PSTPIP2	AR

HPFSs hereditary periodic fever syndromes; *FMF* familial Mediterranean fever; *HIDS* hyperimmunoglobulin D syndrome; *TRAPS* tumor necrosis factor receptor associated periodic syndrome; *CAPS* cryopyrin-associated periodic syndromes; *FCUS* familial cold urticaria syndrome; *MWS*, Muckle-Wells syndrome; *CINCA*, chronic infantile neurologic cutaneous and articular syndrome; *PGA*, pediatric granulomatous arthritis; *BS* Blau syndrome; *EOS* early onset sarcoidosis

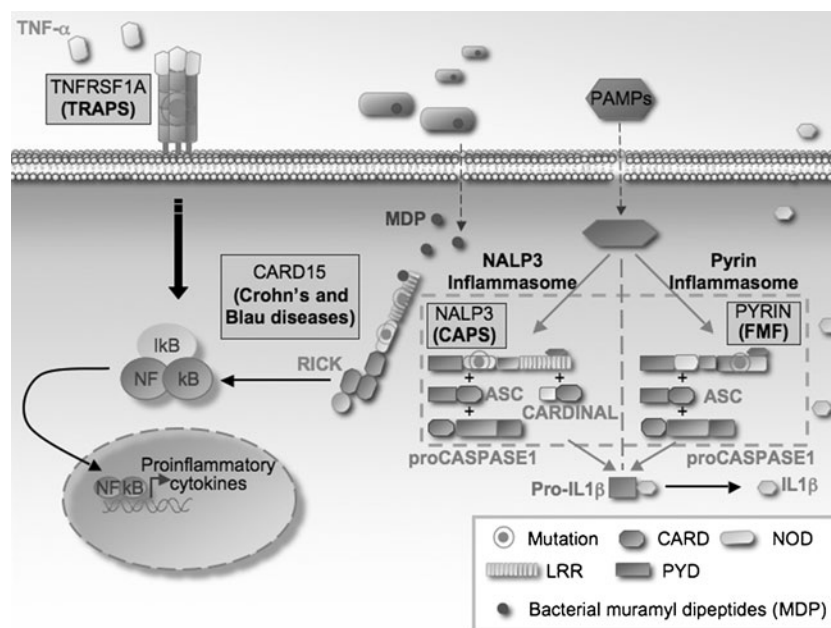


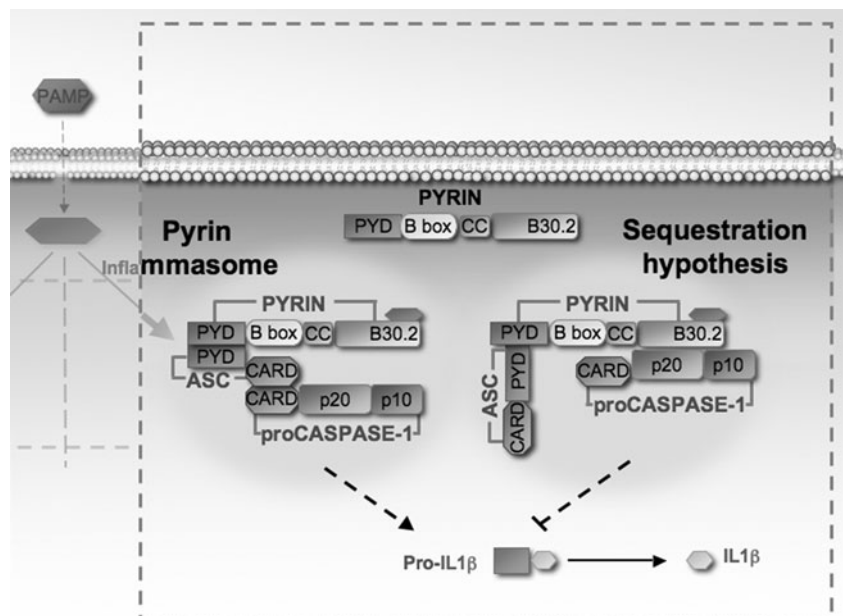
Fig. 2 Pathophysiology of hereditary recurrent febrile syndromes with identified genes. Mutations in the genes encoding TNFRSF1A (*TNFRSF1A*), CARD15 (*CARD15*), cryopyrin (*NALP3*), and pyrin (*MEFV*) are responsible for TRAPS, CARD15-associated, CAPS and FMF diseases, respectively. TNFRSF1A binding to extracellular TNF- α leads to NF- κ B activation. Mutated TNFR1 leads to abnormal signaling. CARD15-associated diseases are due to altered NF κ B regulation. Mutated cryopyrin and pyrin, leading to inflammasome

activation, result in abnormal IL-1 β production. Mutations are denoted by dots. Abbreviations: TNF- α tumor necrosis factor α ; PAMP pathogen-associated molecular pattern; TRAPS TNF-receptor-associated periodic syndrome; CARD15 caspase recruitment domain 15; CAPS cryopyrin-associated periodic syndromes; NLRP3, NLR family, pyrin domain containing; FMF familial Mediterranean fever; PYD pyrin domain; LRR leucine-repeat rich; NOD nucleotide-binding oligomerization domain; CARD caspase recruitment domain

(DCs) and in their endosomes and that can discriminate “self” from microbial “non self” [14] (Fig. 1). DCs are antigen-presenting cells and may promote primary T and B cell responses, therefore representing a crucial link between the innate and adaptive immune system [15].

Following the response of the activated DC subsets, naïve CD4 $^{+}$ T cells may differentiate into different Th subsets with distinct cytokine profiles and effector functions. Th1 and the recently identified Th17 cells produce the proinflammatory cytokines IFN- γ and IL-17, respectively

Fig. 3 Mechanisms of pyrin action. Pyrin inflammasome hypothesis. Pyrin, like cryopyrin, can assemble an inflammasome complex through pyrin–pyrin domain interaction with ASC, resulting in activation of caspase-1. Sequestration hypothesis. Pyrin has an inhibitory effect on IL-1 β caspase-1-mediated activation by a competitive binding of ASC, or of procaspase-1 or caspase-1



[16]. Th1 cells play key roles in inducing B cell and cytotoxic T lymphocyte responses. Research has also shown that Th1 and Th17 are critical mediators in some T cell-mediated autoimmune diseases.

Natural killer (NK) cells may also play a key role in autoimmune responses, by interacting with and providing stimulatory signals for DCs and T cells [17]. Although the exact pathogenetic role of NK cells in the induction of an autoimmune response is still unclear, it has been hypothesized that they may either prevent/limit autoimmune responses, or may have a permissive role in autoimmunity, through suppression and lysis of DCs or activated T cells or by their inappropriate activation, respectively [17].

Microorganisms may integrate their DNA with the human host, provoking possible mutations that may be responsible for autoimmune diseases [18]. For infectious agents, molecular similarity and cross-reactivity may elicit autoimmunity as well [10]. Moreover, self-antigens may be present in the immune system following damage to pericardial and myocardial tissue and cause autoimmune responses. As a consequence of damage to pericardial and myocardial tissue, self-antigens known as damage-associated molecular patterns (DAMPs) may be present in the immune system and may act as endogenous stimuli interacting with TLRs and stimulating B cells, T cells, and antigen-presenting cells [15] (Fig. 1). There may also be a build-up of altered self-antigens attributable to impaired

phagocytosis of apoptotic cells and/or to increased apoptosis, which could stimulate a proinflammatory microenvironment that challenges immune tolerance [19, 20]. By activating surface TLRs on DCs, lingering self-antigens may serve as a signal to autoreactive B cells in germinal centers to survive and mature, and eventually proliferate and differentiate into memory and autoantibody-producing plasma cells [19, 21]. In recurrent pericarditis, the induction of autoimmune responses might therefore depend on several factors, most of them complex and not yet fully understood [6].

Recurrent Pericarditis and Monogenic Autoinflammatory Disorders

IRAP mimics hereditary periodic fever syndromes (HPFSs) since it is characterized by periodic recurrences, alternating with symptom-free intervals with normal acute phase reactants. IRAP patients, like HPFSs patients, feel well between attacks, and also regain their normal daily functions until the next episode occurs. Furthermore, about 10% of IRAP patients have a family history of pericarditis, which suggests a genetic predisposition in some cases [22]. HPFSs are a group of disorders characterized by primary dysfunction of the innate immune system and are mostly caused by mutations of genes involved in the regulation or activation of the inflammatory response without any

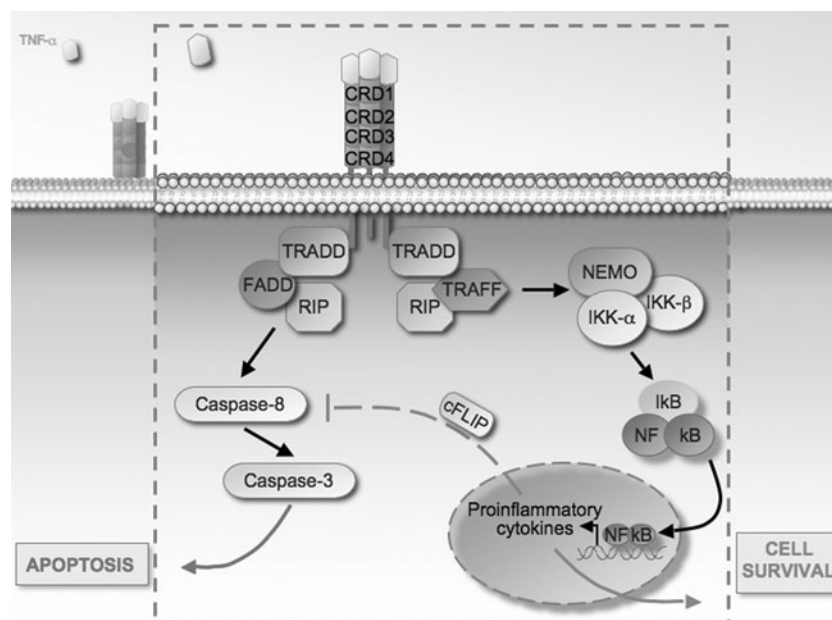


Fig. 4 TNF receptor (TNFR) signaling pathway. TNFRSF1A receptor undergoes trimerization and recruits various adapter molecules resulting in the activation of NF- κ B, which induces several proinflammatory cytokines, survival signal. Upon receptor activation TRAF, is recruited via the adapter TRADD to the plasma membrane, where in complex with RIP activates IKK pathway. This activation

allows the release and nuclear translocation of the NF- κ B thus promoting the transcription of target genes important for cell survival and inflammatory signals. TRADD is also associated with fas-associated death domain (FADD) which leads to the induction of apoptosis via the recruitment and cleavage of procaspase-8. Abbreviations: CRD cysteine-rich extracellular domains

apparent involvement of antigen-specific T cells or significant production of autoantibodies [23, 24]. Table 2 summarizes the main HPFSs and Fig. 2 summarizes their pathogenetic mechanisms.

Among HPFSs, the inflammatory involvement of the serosal membranes is reported both for familial Mediterranean fever (FMF), caused by mutations in the *MEFV* gene which encodes a protein called pyrin [25, 26] (Fig. 3), and for tumor necrosis factor receptor-associated periodic syndrome (TRAPS), caused by mutations in the *TNFRSF1A* gene which encodes the 55-kD receptor for tumor necrosis factor (TNF)- α [27] (Fig. 4). FMF and TRAPS are both characterized by self-limited recurrent fever episodes in association with multi-district inflammation mainly involving the skin, the serosal membranes, and the joints [28]. These disorders usually manifest in the pediatric population, with onset ranging from the first hours to the first decade of life, however a limited number of patients experiences disease onset during adulthood [29–31]. In FMF, the clinical manifestations in adults are similar to those of younger patients [29, 30], whereas patients with adult-onset TRAPS may present incomplete disease and atypical inflammatory responses including cardiac disease such as pericarditis and myocarditis as the only clinical manifestation [32–39].

FMF patients presenting recurrent pericarditis as the sole clinical manifestation have been recently described [40–42]. In contrast, however, we investigated the presence of FMF in three series of Italian patients with recurrent pericarditis; mutations in *MEFV* were searched for respectively in 23, 61, and 30 patients, but no subjects with FMF were discovered [33, 43, 44].

In contrast, we recently described seven recurrent pericarditis patients carrying mutations in the *TNFRSF1A* gene; one of seven carried a novel heterozygous $\Delta Y103-R104$ deletion in the exon 2, five of seven carried a low-penetrance R92Q and one carried a rare V95M mutation [33, 35, 39].

We recently hypothesized that colchicine resistance and/or familial clustering of pericarditis might be two possible criteria for identifying, among IRAP patients, those for whom genetic testing for mutations in the *TNFRSF1A* gene should be carried out [33, 39].

With the aim of improving genetic diagnosis in adult patients suspected with autoinflammatory disorders, we have recently identified some variables that appear to be strongly related to the probability of detecting mutations in the *MEFV* and the *TNFRSF1A* genes, and we have also developed a diagnostic score for identifying patients at high risk to carry these mutations [31]. In addition to the previously suggested criteria [33, 39] our score, since it includes thoracic involvement, might also serve as an evidence-based guideline for identifying among IRAP patients those for whom genetic testing should be carried

out. The validation of the score is currently ongoing with 229 additional patients, and preliminary data showing a high sensitivity (77.8%) and specificity (71.8%) underline its high level of predictiveness (unpublished data, manuscript submitted).

In conclusion, we suggest that familial clustering of pericarditis, together with a poor response to colchicine administration, might be two possible clues for investigating mutations in these patients, although further evaluation involving more patients, different populations and using longitudinal studies are still needed.

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