Published online 2019 August 21.

Immune Profile of Mucosal-Associated Invariant T Cells in Chronic Viral Hepatitis: A Systematic Review and Meta-Analysis

Qinling Liu¹, Feng Zhu¹, Yujing Shi¹ and Dazhi Zhang^{1,*}

¹Department of Infectious Diseases, Key Laboratory of Molecular Biology for Infectious Diseases (Ministry of Education), Institute for Viral Hepatitis, The Second Affiliated Hospital, Chongqing Medical University, Chongqing, China

^{*} *Corresponding author*: Department of Infectious Diseases, Key Laboratory of Molecular Biology for Infectious Diseases (Ministry of Education), Institute for Viral Hepatitis, The Second Affiliated Hospital, Chongqing Medical University, Chongqing, China. Tel: +86-2363829191, Email: 300595@hospital.cqmu.edu.cn

Received 2019 May 24; Revised 2019 July 12; Accepted 2019 August 04.

Abstract

Context: Chronic viral hepatitis (CVH), a world health problem, is the leading cause of hepatocellular carcinoma (HCC). Host immunity plays a critical role in viral clearance, development and progression of the disease. Mucosal-associated invariant T (MAIT) cells represent an abundant form of innate T cells, which plays an essential role in infectious diseases with releasing cytokine, lysing target cells, and shaping adaptive immunity.

Objectives: Although numerous studies showed the immune profiles of MAIT cells in CVH, the results are inconsistent. Thus, we performed a meta-analysis to analyze the immune profiles of MAIT cells in CVH.

Evidence Acquisition: PubMed, Embase, the Cochrane Library, Google Scholar, ScienceDirect, Web of Science, and the China National Knowledge Infrastructure (CNKI) were searched and 10 studies were included. Data from each study were compared using the standardized mean difference (SMD) with 95% confidence interval (CI). The quality assessment of studies and publication bias were evaluated by Newcastle-Ottawa scale and Begg's and Egger's tests, respectively, and a P value of < 0.05 was considered statistically significant.

Results: Meta-analysis of the enrolled studies showed that the frequency of MAIT cells was significantly lower in patients with CVH as compared to healthy controls (SMD = -0.90, 95% CI: -1.32 to -0.48, P < 0.0001). In addition, MAIT cells displayed an activated and exhausted phenotype (CD38: SMD = 0.75, 95% CI: 0.38 to 1.13, P < 0.0001; HLA-DR: SMD = 1.42, 95% CI: 1.02 to 1.83, P < 0.00001; PD-1: SMD = 0.69, 95% CI: 0.13 to 1.26, P = 0.02; CTLA-4: SMD = 0.97, 95% CI: 0.40 to 1.54, P = 0.0008) but not impaired function during CVH (IFN- γ : SMD = 0.04, 95% CI: -0.28 to 0.37, P = 0.79; TNF- α : SMD = -0.80, 95% CI: -1.77 to 0.16, P = 0.10; Granzyme B: SMD = -0.14, 95% CI: -0.58 to 0.29, P = 0.53; Perforin: SMD = -0.27, 95% CI: -0.87 to 0.33, P = 0.38).

Conclusions: In CVH patients, MAIT cells are significantly depleted in the peripheral bloodstream and displayed an activated and exhausted phenotype; however, the reduction of peripheral blood MAIT cells accompanied by activated and exhausted phenotypes may not impair the cytolytic function and cytokine production of these cells.

Keywords: Chronic Viral Hepatitis, Mucosal-Associated Invariant T Cells, Meta-Analysis

1. Context

Chronic viral hepatitis (CVH) is a chronic inflammation of the liver. Several types of human viral hepatitis cause infection either through enteric-transmission (hepatitis A and E) or blood transfusion (hepatitis B, C, and D). Hepatitis A and E are host-controlled infections that do not progress to chronic infection (except for hepatitis E), while hepatitis B, C, and D often progress to persistent chronic infection (1). Hence, host immunity (innate and adaptive) is responsible for the development and progression of diseases. An estimated 257 and 71 million people are living with chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infection, respectively (WHO 2015 - 2017) (2), making CVH the leading cause for hepatocellular carcinoma (HCC) (60% - 70%) globally, with a total incidence of 16/100000 (3).

Human mucosal-associated invariant T (MAIT) cells were originally identified in 1993, with semi-invariant TCR TRAV1-2/TRAJ33 expression (4). Treiner et al. observed that the canonical hV α 7.2-J α 33 or mV α 19-J α 33 TCR rearrangement was preferentially located in the gut lamina propria of humans and therefore, named these cells MAIT cells (5). MAIT cells constitute a subpopulation of T cells, including intrahepatic (10% - 40%) and peripheral blood CD 3⁺T cells (0.1% -10%)(6,7). Moreover, they develop in the thymus and migrate to the periphery to become the antigen-specific $\alpha\beta$ T-cell population in the human immune system (8).

Copyright © 2019, Author(s). This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License (http://creativecommons.org/licenses/by-nc/4.0/) which permits copy and redistribute the material just in noncommercial usages, provided the original work is properly cited.

Koay et al. reported PLZF as a controlling transcription factor for three developmental stages of maturation and function of MAIT cells (9). Most studies have defined MAIT cells as CD3⁺CD161^{high} V α 7.2+ lymphocytes (10-13). MAIT cells recognize Vitamin B2 (riboflavin) metabolites produced by bacteria and yeasts in a major histocompatibility complexrelated protein 1 (MR1)-dependent manner (14, 15) and can be activated in an MR1-independent fashion in response to cytokines (7, 16-18). Additionally, MR1 presenting antigen is recognized by MAIT cells using their TCRs (19). Upon TCRdependent or TCR-independent activation, MAIT cells produce pro-inflammatory cytokines (IFN- γ , TNF- α), cytolytic products (perforin, granulysin and granzymes) and degranulate (exposing CD107a to the cell surface) (20).

MAIT cells have been widely studied in infectious diseases. It is one of the key immune controllers of gut microbiota, fungal infection, bacterial infection, and inflammatory diseases (21, 22). A recently published study showed a lower frequency of MAIT cells, with increased expression of immune exhaustion and chronic immune activation in chronic HCV-infected patients (23). Yong et al. reported the frequency of MAIT cells were significantly reduced (12), while Boeijen et al. reported that MAIT cells were not deleted or functionally impaired in chronic hepatitis B (CHB) patients (24).

2. Objectives

Considering the above reports, we aimed to perform a systematic review and meta-analysis to explore the frequency, phenotype, and function of MAIT cells in patients with CVH.

3. Evidence Acquisition

Our meta-analysis is reported in accordance with the PRISMA (preferred reporting items for systematic reviews and meta-analyses) statement.

3.1. Literature Search

The following electronic databases were used: PubMed, Embase, the Cochrane Library, Google Scholar, ScienceDirect, Web of Science, and the China National Knowledge Infrastructure (CNKI) for all appropriate articles, which published before 25 June 2019. The search strategy and the search terms were developed with the support of two independent reviewers (Qinling Liu and Feng Zhu). The used MeSH (Medical Subject Headings) terms and text words were: "mucosal associated invariant T cells", "MAIT cells", "chronic viral hepatitis", "chronic hepatitis b", "chronic hepatitis c", and "chronic hepatitis d". The language of the enrolled studies was restricted to English or Chinese.

3.2. Selection of Articles

The inclusion criteria were as follows: (a) treatmentfree patients with CVH (i.e., patients did not take antiviral therapy or immunosuppressive drugs 6 months before the sampling); (b) the study design: case-control or cohort; (c) study details: frequency, phenotypes or functions of MAIT cells in the peripheral blood or liver tissue.

The following studies were excluded: (a) study of patients co-infected with human immunodeficiency virus; (b) study did not involve healthy controls; (c) duplication or overlapping study; (d) book chapter, review articles or meta-analysis. Our selection decisions were not influenced by the names of the authors or journals of the articles. Third investigator (Dazhi Zhang) was invited to provide arbitration when there was a divergence between two reviewers.

3.3. Data Extraction

The two reviewers scanned the titles and abstracts of all search results independently, and those satisfied the inclusion criteria were selected for full-text review. The final inclusion or exclusion decisions were made by inspecting the full manuscripts. The following data were extracted from each paper: first author and published year, country, type of study design, number of patients and healthy control, characteristics of patients and healthy control, and the results measured by flow cytometry (including frequency, phenotype, and function of MAIT cells). Emails were sent to the corresponding, or co-corresponding authors if the information of the studies were unclear. In addition, if there were no email replies from the authors, the software GetData Graph Digitizer 2.22 was used to get data from the articles.

3.4. Quality Assessment and Risk of Bias

The Newcastle-Ottawa Scale (NOS) was applied for assessing the quality of studies (Wells et al., 2014) (25). The score of NOS ranged from zero to nine points, and the assessment of study quality is shown in Table 1. The publication bias of the meta-analysis was evaluated with Begg's and Egger's tests using STATA version 15.1

3.5. Statistical Analysis

After collecting and converting, data of the included studies were combined by meta-analyses using Review Manager 5.3 (The Nordic Cochrane Centre, The Cochrane

Table 1. Assessment of Study Quality					
Study	Study Type	Selection	Comparability	Exposure/Outcome	Total
Provine et al. (26), 2018	Case-control	***	*	**	*****
Yong et al. (27), 2018	Case-control	***	**	**	******
Setsu et al. (28), 2017	Case-control	**	*	**	*****
Boeijen et al. (24), 2017	Case-control	**	**	**	******
Beudeker et al. (29), 2018	Case-control	**	**	**	*****
Bolte et al. (30), 2017	Cohort	***	*	***	*****
Dias (31), 2019	Case-control	**	**	**	*****
Spaan et al. (32),2016	Cohort	***	**	***	*******
van Wilgenburg et al. (33), 2016	Case-control	***	*	**	******
Barathan et al. (23), 2015	Case-control	***	**	**	******

Collaboration, 2012). $I^2 > 50\%$ indicated there was significant heterogeneity then random effects model was applied, otherwise affixed effects model was applied (34). Standard mean difference (SMD) with a 95% confidence interval (CI) was used to analyze continuous variables, including frequency, phenotype, and function of MAIT cells. A P value of < 0.05 was considered statistically significant.

4. Results

4.1. Search Results and Study Characteristics

Flow diagram of study selection is shown in Figure 1. A total of 848 studies were identified adopting the search strategy. Of these twenty-one publications were from PubMed, 57 from Embase, 46 from Web of Science, 2 from Cochrane Library, 620 from Google scholar, 101 from ScienceDirect and 1 publication was identified from CNKI. After removing 186 duplicates and excluding 226 review, 53 book chapter, and 363 irrelevant records, 20 full-text were assessed for eligibility. One letter and one abstract of congresses were removed because of poor quality. Four fulltext articles were excluded because of having no data of interest and four studies were excluded because of no way to extract data. Finally, ten studies were included in the metaanalysis (23, 24, 26-33).

The characteristics of the included studies are listed in Table 2. Among the final inclusion, eight studies were casecontrol studies and two were cohort studies. Three studies were from the Netherlands, two studies were from the United Kingdom, two from Malaysia, one from Japan, one from the USA, and one from Sweden.

4.2. Frequency of Peripheral MAIT Cells

The meta-analysis of the 9 studies showed that there was a significantly lower frequency of peripheral MAIT

cells in CVH patients compared with healthy control (SMD = -0.90, 95% CI: -1.32 to -0.48, P < 0.0001; Figure 2). The I² value was 74% indicating significant heterogeneity and random effect model was applied. One study identified MAIT cells by different gating orders, which may result in significant heterogeneity. There was no significant difference in the frequency of MAIT cells in chronic hepatitis B subgroup compared with healthy controls (SMD = -0.41, 95% CI: -0.91 to 0.09, P = 0.11). The I² value was 0% indicating no significant heterogeneity and fixed effects model was applied. The frequency of MAIT cells was significantly lower in chronic hepatitis C subgroup than healthy control (SMD = -1.18, 95% CI: -1.69 to -0.67, P < 0.00001). The I² value was 75%, indicating significant heterogeneity and random effects model was applied.

4.3. Phenotype of Peripheral MAIT Cells

To investigate the phenotype of MAIT cells, the expression of HLA-DR, CD38, CD57, PD-1, TIM-3, and CTLA-4 of MAIT cells in the blood of patients with CVH and healthy controls were analyzed (Figure 3). The pooled SMD of the CD38 expression showed there was a significantly higher level of MAIT cells in patients with CVH than healthy controls (SMD = 0.75, 95% CI: 0.38 to 1.13, P < 0.0001). The I^2 value was 0%, indicating no statistical heterogeneity and the fixed effects model was applied. A meta-analysis of the four studies that evaluated HLA-DR also showed MAIT cell levels were significantly higher in patients with CVH than healthy controls (SMD = 1.42, 95% CI: 1.02 to 1.83, P < 0.00001). The I^2 value was 43%, indicating no statistical heterogeneity and the fixed effects model was applied. Meta-analysis of CD57 showed no significant difference between the two groups (SMD = 2.11, 95% CI: -0.27 to 4.50, P = 0.08). Meta-analysis of two studies that evaluated PD-1 and CTLA-4 showed a significant difference between patients with CVH and healthy controls (PD-1: SMD = 0.69, 95% CI: 0.13 to 1.26, P = 0.02;



CTLA-4: SMD = 0.97, 95% CI: 0.40 to 1.54, P = 0.0008). However, there was no significant difference in the expression of TIM-3 (SMD = 0.56, 95% CI: 0.01 to 1.12, P = 0.05). In conclusion, MAIT cells displayed an activated and exhausted phenotype during CVH.

4.4. Function of Peripheral MAIT Cells

MAIT cells respond to antigen (TCR-dependent) and cytokine (TCR-independent) stimulation by producing proinflammatory cytokines, including IFN- γ , TNF- α , and IL-17, and exert cytotoxic effector functions by releasing granzyme B and perforin (6). We evaluated IFN- γ , TNF- α , perforin, and granzyme B production of peripheral MAIT cells in patients with CVH and the healthy controls (Figure 4). There was no difference in IFN- γ and TNF- α production with MAIT cells in patients with CVH and healthy con-

trols (IFN- γ : SMD = 0.04, 95% CI: - 0.28 to 0.37, P = 0.79; TNF- α : SMD = -0.80, 95% CI: -1.77 to 0.16, P = 0.10). I² were 19% and 72%, and fixed effects model and random effects model were applied, respectively. Additionally, there was also no difference in perforin and granzyme B releasing (perforin: SMD=-0.27, 95% CI:-0.87 to 0.33, P=0.38; granzyme B:SMD= -0.14, 95% CI:-0.58 to 0.29, P=0.53). I² were 0% and 25%, indicating no statistical heterogeneity and fixed effects model was applied. Therefore, the meta-analysis of the function of MAIT cells showed no significant difference between patients with CVH and healthy controls.

4.5. Publication Bias

The publication bias of the meta-analysis was assessed by Begg's tests and Egger's tests. The result showed no significant publication bias in this study (Figure 5).

Table 2. Characteristics of Enrolled Studies				
Study, Patients No.	Age in Years	Male,%	ALT (U/I)	HBV-DNA or HCV-RNA
Provine et al. (26), 2018, United Kingdom				
Healthy controls: 16	NA	NA	NA	-
Chronic HCV: 33	$45(20-76)^{a}$	54.55	59 (21 - 206) ^a	NA
Yong et al. (27), 2018, Malaysia				
Healthy controls: 13	$44(40-51)^{b}$	61.5	NA	-
HBV-DNA + ve: 12	50 (47.3 - 57.3) ^b	50	$26.5(18.3-40.3)^{b}$	20377 (3468 - 326353) ^{b, g}
HBV-DNA - ve: 9	55 (38 - 61) ^b	66.7	$45(20-36.5)^{b}$	-
Setsu et al. (28), 2017, Japan				
Healthy controls: 13	$66(44 - 83)^{a}$	57.89	$47(11-209)^{a}$	-
Chronic viral hepatitis: 19	52 (30 - 81) ^a	61.54	$14(9-26)^{a}$	NA
Boeijen et al. (24), 2017, The Netherlands				
Healthy controls: 17	41 ^h	64.71	NA	-
Chronic hepatitis B: 18	$43(25-59)^{c}$	72.22	58 (14 - 366) ^c	7.61 (2.46 - 8.57) ^{c, f}
Beudeker et al. (29), 2018, The Netherlands				
Healthy controls: 9	$40(28-50)^{e}$	100	NA	-
HCV F0- F1: 9	54 (45 - 68) ^e	100	57 (24 - 95) ^e	$4.38 imes 10^{6e, f}$
HCV F3- F4: 11	51 (47 - 57) ^e	100	100(38 - 211) ^e	$2.90 imes 10^{6e, f}$
Bolte et al. (30), 2017, USA				
Healthy controls: 42	NA	NA	NA	-
Chronic HCV: 56	59 (55.0 - 62.3) ^b	57	$67(36-128)^{\mathrm{b}}$	6.4 (5.6 - 5.9) ^{b, f}
Dias et al. (31), 2019, Sweden				
Healthy controls: 57	42 (21 - 65) ^a	46	NA	-
Chronic hepatitis B: 38	$42(26-74)^{a}$	28	$26(9-98)^{a}$	341 (5 - 33000000) ^{a, g}
Chronic HDV: 41	38 (19 - 61) ^a	51	$76(31-360)^{a}$	HDV: 94190 $(0 - 23000000)^{a, g}$; HBV: 152 $(0 - 1.1E + 09)^{a, h}$
Spaan et al. (32),2016 The, Netherlands				
Healthy controls: 22	$54(42-70)^{c}$	67	NA	-
CHCV PegIFN/riba: 11	$45(27-60)^{c}$	73	79 (34 - 164) ^c	6.66 (2.57 - 7.43) ^{c, f}
CHCV PegIFN/riba/telaprevir: 11	50 (25 - 61) ^c	82	70 (29 - 140) ^c	6.41 (4.54 - 6.91) ^{c, f}
CHCV Asunaprevir/daclatasvir: 5	52 (43 - 66) ^c	80	188 (94 - 269) ^c	6.08 (5.2 - 6.36) ^{c, f}
CHCV Sofosbuvir/daclatasvir: 6	59 (36 - 70) ^c	67	126 (24 - 196) ^c	6.43 (4.92 - 6.72) ^{c, f}
van Wilgenburg et al. (33), 2016, United Kingdom				
Healthy controls:23	NA	NA	NA	-
Chronic HCV: 17	51 (32 - 68) ^c	58.82	NA	NA
Barathan et al. (23), 2015, Malaysia				
Healthy controls: 25	26 (24 - 33) ^c	NA	NA	-
Chronic HCV: 25	40 (29 - 55) ^c	60	NA	151613 (15 - 1310000) ^{c, g}

^aMedian (range). ^bMedian (IQR).

⁶Median (IQR). ⁶Mean (range). ⁴Mean. ⁹Unspecified mean or median. ^fLog₁₀IU/mL. ^gCopies/mL. ^hIU/mL.

5. Conclusions

Our study is the first attempt to review the original study in order to provide a comprehensive estimate of abnormal immune profiles of MAIT cells in CVH. MAIT cells in patients with CVH displayed an activated and exhausted phenotype, which might lead to the reduction of MAIT cells

A. Chronic Viral I	lepatitis								
	Chron	ic Viral Hep	oatitis	Hea	althy Contr	ol		Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
Barathan, 2016	54.7727	13.636	25	82.0455	6.818	25	10.3%	-2.49 [-3.24, -1.74]	
Beudeker, 2018	0.827826	0.361109	23	3.355	2.826685	14	10.4%	-1.42 [-2.16, -0.67]	
Boeijen, 2017	2.804732	4.087882	18	3.692722	4.311837	17	11.1%	-0.21 [-0.87, 0.46]	
Bolte, 2017	1.604885	1.311213	37	2.830154	2.321533	57	13.3%	-0.61 [-1.03, -0.19]	
Provine, 2018	1.108	1.071	18	2.765	2.978	16	10.8%	-0.74 [-1.44, -0.04]	
Setsu, 2017	1.57201	2.5355	19	1.77485	2.12982	13	10.7%	-0.08 [-0.79, 0.62]	
Spaan, 2016	0.480508	0.499313	33	1.455235	1.334076	22	11.9%	-1.04 [-1.61, -0.46]	
Wilgenburg, 2016	2.45658	3.68317	17	7.628658	6.012836	23	11.1%	-0.98 [-1.65, -0.32]	
Yong, 2018	2.063476	1.493145	20	3.070299	1.44253	11	10.3%	-0.66 [-1.42, 0.09]	
Total (95% CI)			210			198	100.0%	-0.90 [-1.32, -0.48]	◆
Heterogeneity: Tau ² =	0.30; Chi ² =	: 30.71, df = 8	B (P = 0.0	0002); I ² = 7	4%				
Test for overall effect:	Z= 4.16 (P	< 0.0001)							-2 -1 U 1 Z
B Chronic Honor	141a D								Chronic Viral Repatitis Reality Control
D. Chronic Hepat			_						
	Chroni	c Hepatitis	В	Hea	Ithy Contro	DI		Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% Cl
Boeijen, 2017	2.804732	4.087882	18	3.692722	4.311837	17	56.4%	-0.21 [-0.87, 0.46]	
Yong, 2018	2.063476	1.493145	20	3.070299	1.44253	11	43.6%	-0.66 [-1.42, 0.09]	
Total (95% CI)			38			28	100.0%	-0.41 [-0.91, 0.09]	· · · · · · · · · · · · · · · · · · ·
Heterogeneity: Chi ² =	0.79, df = 1	(P = 0.37); F	²=0%						
Test for overall effect	: Z=1.59 (P	= 0.11)							Chronic Hepatitis B Healthy Control
C									
. Chronic Hepat	itis C Chroni	c Hepatitis	с	Hea	Ithy Contro	ы		Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
Barathan, 2016	54.7727	13.636	25	82.0455	6.818	25	15.2%	-2.49 [-3.24, -1.74]	
Beudeker, 2018	0.827826	0.361109	23	3.355	2.826685	14	15.3%	-1.42 [-2.16, -0.67]	
Bolte, 2017	1.604885	1.311213	37	2.830154	2.321533	57	19.6%	-0.61 [-1.03, -0.19]	
Provine, 2018	1.108	1.071	18	2.765	2.978	16	15.9%	-0.74 [-1.44, -0.04]	
Spaan, 2016	0.480508	0.499313	33	1.455235	1.334076	22	17.6%	-1.04 [-1.61, -0.46]	
Wilgenburg, 2016	2.45658	3.68317	17	7.628658	6.012836	23	16.4%	-0.98 [-1.65, -0.32]	
Total (95% CI)			153			157	100.0%	-1.18 [-1.69, -0.67]	◆
Heterogeneity: Tau ² =	= 0.30; Chi ^z :	= 19.92, df =	5 (P = 0	.001); I ^z = 7	5%				
Test for overall effect	Z = 4.52 (P	< 0.00001)							
		,							Chronic Hepatitis C Healthy Control

Figure 2. Frequency of peripheral MAIT cells is shown.

in peripheral blood; nevertheless, no impairment was seen in MAIT cells' function compared to healthy controls.

Given the essential role of MAIT cells in infectious diseases and inconsistent results of available studies, we performed a meta-analysis to investigate the immune profiles of MAIT cells in CVH. Our study shows that the frequency of peripheral MAIT cells in patients with CVH was significantly reduced compared to healthy controls. In line with our findings, previous studies have also shown the level of peripheral MAIT cells were significantly lower in infectious diseases such as HIV infection (35) and primary biliary cholangitis (10). MAIT cells have been reported to home to peripheral tissues, especially the intestine and the liver with high expression of chemokine receptors CCR5, CCR6, and CXCR6 (36). Previous studies showed that the disappearance of MAIT cells from the peripheral blood was associated with modified expression of chemokine receptors (10, 23). MAIT cells are also identified as IL-18R⁺V α 7.2⁺ T-cell population, significantly losing their CD161 expression in HIV-infected patients compared with uninfected controls (11). This suggests that increasing MAIT cells are recruited to inflammatory sites and down-regulation of CD161 may lead to the reduction of peripheral blood MAIT cells in patients with CVH.

In agreement with current studies, MAIT cells display an activated and exhausted phenotype in patients with CVH, with higher levels of immune activation markers (CD38 and HLA-DR) and inhibitory markers (PD-1 and CTLA-4). MAIT cells are unable to recognize viruses in TCRdependent way due to insufficient production of Vitamin B2 (riboflavin) metabolites. However, viruses can activate MAIT cells via stimulating cytokine production. Some researchers also point out that viruses activate MAIT cells by stimulating cytokine release via ligation of toll-likereceptors (TLRs) or other pattern recognition receptors (PRRs) (37). TLR8 agonist, ssRNA40, can indirectly activate MAIT cells dependent on IL-12 and IL-18 production intrahepatic monocytes (38). Overactivation of MAIT cells may also progress to apoptosis, leading to the reduction of MAIT cells.

Contrary to our expectation, the function of MAIT cells was not impaired in patients with CVH compared to healthy controls. Co-culturing MAIT cells with non-typeable Haemophilus influenzae-infected macrophages (18) or Francisella novicida-infected macrophages (39) can activate MAIT cells. A study also showed that DENV,

1.0000	Chronie	c Viral Hepa	atitis	Heal	thy Contro	bl		Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Beudeker, 2018	19.65444	21.2862	9	2.665556	1.929094	9	13.8%	1.07 [0.07, 2.08]	
Boeijen, 2017	7.800031	5.74026	18	4.503169	5.453507	17	30.2%	0.57 [-0.10, 1.25]	+
Spaan, 2016	16.89809	6.85327	33	13.59352	4.315948	12	31.0%	0.52 [-0.15, 1.19]	
Yong, 2018	28.66829	18.94717	21	11.42111	5.751698	13	25.0%	1.09 [0.35, 1.84]	
Total (95% CI)			81			51	100.0%	0.75 [0.38, 1.13]	
Heterogeneity: Chi ² = Test for overall effect:	1.94, df = 3 Z = 3.97 (P	(P = 0.59); P < 0.0001)	= 0%						-4 -2 0 2 Chronic Viral Handtitic Healthy Control
									Chronic viral nepatitis nearthy Control
B . CD57									
~	Chroni	c Viral Hepa	atitis	Heal	thy Contro) Trans		Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD 000004	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Boeijen, 2017 Vong. 2019	25.52989	31.00331	10	5.615942	2.066528	12	50.9%	0.92 [0.03, 1.81]	· · · · · · · · · · · · · · · · · · ·
rong, 2018	38.52563	13.38425	21	1.90987	1.9098/4	13	49.1%	3.33 [2.20, 4.43]	-
Total (95% CI)			31			25	100.0%	2.11 [-0.27, 4.50]	
Heterogeneity: Tau ² =	: 2.70; Chi ² =	11.42, df =	1 (P = 0.	0007); I ² = 9	1%				-10 -5 0 5 10
Test for overall effect	Z=1.74 (P	= 0.08)							Chronic Viral Hepatitis Healthy Control
C									
. HLA-DR	Chroni	c Viral Hepa	atitis	Heal	thy Contro	ol .		Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Barathan, 2016	29.34356	17.04398	25	5.200182	6.020421	25	36.5%	1.86 [1.19, 2.53]	
Beudeker, 2018	6.049392	4.507591	9	2.814817	2.306727	9	17.3%	0.86 [-0.12, 1.84]	—
Boeijen, 2017	5.59618	4.731057	10	2.773988	1.671528	12	21.4%	0.80 (-0.08, 1.68)	
Yong, 2018	20.23473	9.545669	21	5.975129	5.111475	13	24.8%	1.70 [0.89, 2.52]	
Total (95% CD			66			50	100.0%	4 42 (4 02 4 92)	
10101 (0077 01)			00			29	100.0%	1.42 [1.02, 1.03]	
Heterogeneity: Chi ² =	5.30, df = 3	(P = 0.15); P	= 43%			29	100.0%	1.42 [1.02, 1.03]	
Heterogeneity. Chi ² = Test for overall effect:	5.30, df = 3 Z = 6.86 (P	(P = 0.15); i² < 0.00001)	= 43%			59	100.0%	1.42 [1.02, 1.03]	-4 -2 0 2 4 Chronic Viral Hepatitis Healthy Control
Heterogeneity: Chi ² = Test for overall effect	5.30, df = 3 Z = 6.86 (P	(P = 0.15); P < 0.00001)	= 43%			29	100.0%	1.42 [1.02, 1.63]	- 1 - 1 - 1 - 1 - 1 - 1 - 1 - 1 - 1 - 1
Heterogeneity: Chi ^p = Test for overall effect: D . PD-1	5.30, df = 3 Z = 6.86 (P	(P = 0.15); P < 0.00001)	= 43%	Heal	thy Contro	59	100.0%	1.42 [1.02, 1.03]	
Heterogeneity: Chi ² = Test for overall effect D. PD-1 Study or Subgroup	5.30, df = 3 Z = 6.86 (P Chronie Mean	(P = 0.15); P < 0.00001) c Viral Hepa SD	atitis Total	Heal Mean	thy Contro SD	ol Total	S Weight	1.42 [1.02, 1.63] Rd. Mean Difference IV. Fixed, 95% Cl	
Heterogeneity: Chi ² = Test for overall effect D . PD-1 <u>Study or Subgroup</u> Boeijen, 2017	5.30, df = 3 Z = 6.86 (P Chronie <u>Mean</u> 17.7904	(P = 0.15); P < 0.00001) c Viral Hepa <u>SD</u> 12.50488	43% atitis <u>Total</u>	Heal <u>Mean</u> 14.43603	thy Contro 50 6,390273	ol <u>Total</u> 12	S Weight 44.2%	1.42 [1.02, 1.85] Rd. Mean Difference IV. Fixed. 95% Cl 0.33 [-0.51, 1.18]	-4 -2 0 2 4 Chronic Viral Hepatitis Healthy Control Std. Mean Difference IV. Fixed, 95% C1
Heterogeneity. Chi ^p = Test for overall effect D. PD-1 Study or Subgroup Boeijen, 2017 Yong, 2018	5.30, df = 3 Z = 6.86 (P Chronic Mean 17.7904 27.98	(P = 0.15); P < 0.00001) c Viral Hepa <u>SD</u> 12.50488 14.42	atitis <u>Total</u> 10 21	Heal <u>Mean</u> 14.43603 15.25	thy Contro SD 6.390273 8.73	59 1 <u>Total</u> 12 12	S <u>Weight</u> 44.2% 55.8%	Ad. Mean Difference IV. Fixed, 95% CI 0.33 [0.51, 1.18] 0.98 (0.23, 1.73]	-4 -2 0 2 4 Chronic Viral Hepatitis Healthy Control Std. Mean Difference IV, Fixed, 95% Cl
Heterogeneity. Chi ^p = Test for overall effect D. PD-1 Study or Subgroup Boeijen, 2017 Yong, 2018	5.30, df = 3 Z = 6.86 (P Chronic Mean 17.7904 27.98	(P = 0.15); P < 0.00001) c Viral Hepa <u>SD</u> 12.50488 14.42	atitis <u>Total</u> 10 21	Heal <u>Mean</u> 14.43603 15.25	thy Contro SD 6.390273 8.73	ol Total 12 12	S <u>Weight</u> 44.2% 55.8%	142 [1.02, 1.03] 14. Mean Difference <u>IV. Fixed, 95% Cl</u> 0.33 [-0.51, 1.18] 0.98 [0.23, 1.73]	-4 -2 0 2 4 Chronic Viral Hepatitis Healthy Control Std. Mean Difference IV, Fixed, 95% Cl
Heterogeneity. ChP = Test for overall effect D. PD-1 Study or Subgroup Boeijen, 2017 Yong, 2018 Total (95% CI)	5.30, df = 3 Z = 6.86 (P Chronic Mean 17.7904 27.98	(P = 0.15); P < 0.00001) c Viral Hepa <u>SD</u> 12.50488 14.42	65 = 43% atitis Total 10 21 31	Heal <u>Mean</u> 14.43603 15.25	thy Contro SD 6.390273 8.73	59 11 12 12 24	S Weight 44.2% 55.8% 100.0%	Nd. Mean Difference IV. Fixed, 95% CI 0.33 [-0.51, 1.18] 0.98 [0.23, 1.73] 0.69 [0.13, 1.26]	Chronic Viral Hepatitis Healthy Control Std. Mean Difference N. Fixed, 95% Cl
Heterogeneity. ChP = Test for overall effect D. PD-1 Study or Subgroup Boeijen, 2017 Yong, 2018 Total (95% Cl) Heterogeneity. ChP =	5.30, df = 3 Z = 6.86 (P Chronie Mean 17.7904 27.98 1.24, df = 1	(P = 0.15); P < 0.00001) c Viral Hepa <u>SD</u> 12.50488 14.42 (P = 0.27); P = 0.02)	atitis Total 10 21 31 = 19%	Heal <u>Mean</u> 14.43603 15.25	thy Contro SD 6.390273 8.73	59 Total 12 12 24	S Weight 44.2% 55.8% 100.0%	Ad. Mean Difference <u>IV. Fixed, 95% CI</u> 0.33 [-0.51, 1.18] 0.98 [0.23, 1.73] 0.69 [0.13, 1.26]	Chronic Viral Hepatitis Healthy Control Std. Mean Difference IV. Fixed, 95% C1
Heterogeneity. ChP = Test for overall effect D. PD-1 Study or Subgroup Boeijen, 2017 Yong, 2018 Total (95% Cl) Heterogeneity. ChP = Test for overall effect	5.30, df = 3 Z = 6.86 (P Chronie Mean 17.7904 27.98 1.24, df = 1 Z = 2.42 (P	(P = 0.15); P < 0.00001) c Viral Hepa SD 12.50488 14.42 (P = 0.27); P = 0.02)	atitis <u>Total</u> 10 21 31 = 19%	Heal <u>Mean</u> 14.43603 15.25	thy Contro SD 6.390273 8.73	59 Total 12 12 24	S <u>Weight</u> 44.2% 55.8% 100.0%	Ad. Mean Difference <u>IV. Fixed, 95% C1</u> 0.33 [-0.51, 1.18] 0.98 [0.23, 1.73] 0.69 [0.13, 1.26]	Chronic Viral Hepatitis Healthy Control
Heterogeneity. ChP = Test for overall effect D. PD-1 Study or Subgroup Boeijen, 2017 Yong, 2018 Total (95% Cl) Heterogeneity. ChP = Test for overall effect	5.30, df = 3 Z = 6.86 (P Chronic Mean 17.7904 27.98 1.24, df = 1 Z = 2.42 (P	(P = 0.15); P < 0.00001) c Viral Hepa SD 12.50488 14.42 (P = 0.27); P = 0.02)	atitis <u>Total</u> 10 21 31 = 19%	Heat <u>Mean</u> 14.43603 15.25	thy Contro SD 6.390273 8.73	59 11 12 12 24	S <u>Weight</u> 44.2% 55.8% 100.0%	Ad. Mean Difference <u>IV. Fixed, 95% CI</u> 0.33 [-0.51, 1.18] 0.98 [0.23, 1.73] 0.69 [0.13, 1.26]	Chronic Viral Hepatitis Healthy Control
Heterogeneity, ChP = Test for overall effect D. PD-1 Study or Subgroup Boeijen, 2017 Yong, 2018 Total (95% Cl) Heterogeneity, ChP = Test for overall effect E. TIM-3	5.30, df = 3 Z = 6.86 (P Chronii <u>Mean</u> 17.7904 27.98 1.24, df = 1 Z = 2.42 (P Chronii	(P = 0.15); P < 0.00001) c Viral Hepa SD 12.50488 14.42 (P = 0.27); P = 0.02) c Viral Hepa	atitis <u>Total</u> 10 21 31 = 19%	Hean <u>Mean</u> 14.43603 15.25 Heal	thy Contro SD 6.390273 8.73 thy Contro	59 101 12 12 24	S Weight 44.2% 55.8% 100.0%	Ad. Mean Difference <u>IV. Fixed, 95% C1</u> 0.33 [-0.51, 1.18] 0.98 [0.23, 1.73] 0.69 [0.13, 1.26] Std. Mean Difference	Chronic Viral Hepatitis Healthy Control Std. Mean Difference M. Fixed, 95% Cl -4 Chronic Viral Hepatitis Healthy Control Std. Mean Difference Std. Mean Difference
Heterogeneily. ChP = Test for overall effect D. PD-1 Study or Subgroup Boeijen, 2017 Yong, 2018 Total (95% Cl) Heterogeneily. ChP = Test for overall effect E. TIM-3 Study or Subgroup	5.30, df = 3 Z = 6.86 (P Chronii <u>Mean</u> 17.7904 27.98 1.24, df = 1 Z = 2.42 (P Chronii <u>Mean</u>	(P = 0.15); P < 0.00001) c Viral Hepa SD 12.50488 14.42 (P = 0.27); P = 0.02) c Viral Hepa SD	atitis <u>Total</u> 10 21 31 = 19% atitis <u>Total</u>	Heal <u>Mean</u> 14.43603 15.25 Heal <u>Mean</u>	thy Contro SD 6.390273 8.73 thy Contro	ol <u>Total</u> 12 12 24 <u>Total</u>	S Weight 44.2% 55.8% 100.0%	Ad. Mean Difference <u>IV. Fixed. 95% C1</u> 0.33 [-0.51, 1.18] 0.98 [0.23, 1.73] 0.69 [0.13, 1.26] Std. Mean Difference <u>IV. Fixed. 95% C1</u>	Chronic Viral Hepatitis Healthy Control Std. Mean Difference N. Fixed, 95% Cl Chronic Viral Hepatitis Healthy Control Std. Mean Difference N. Fixed, 95% Cl
Heterogeneily. ChP = Test for overall effect D. PD-1 Study or Subgroup Boeijen, 2017 Yong, 2018 Total (95% CI) Heterogeneily. ChP = Test for overall effect E. TIM-3 Study or Subgroup Boeijen, 2017	5.30, df = 3 Z = 6.86 (P Chronii <u>Mean</u> 17.7904 27.98 1.24, df = 1 Z = 2.42 (P Chronii <u>Mean</u> 1.828996 00 0010	(P = 0.15); P < 0.00001) c Viral Hepa <u>SD</u> 12.50488 14.42 (P = 0.27); P = 0.02) c Viral Hepa <u>SD</u> 3.286539	atitis <u>Total</u> 10 21 31 = 19% atitis <u>Total</u>	Heal <u>Mean</u> 14.43603 15.25 Heal <u>Mean</u> 0.570012	thy Contro SD 6.390273 8.73 thy Contro SD 0.585821	59 11 12 12 24 12 24	S Weight 44.2% 55.8% 100.0% Weight 41.7%	1.42 [1.02, 1.03] Rd. Mean Difference IV. Fixed, 95% CI 0.33 [-0.51, 1.18] 0.96 [0.23, 1.73] 0.69 [0.13, 1.26] Std. Mean Difference IV. Fixed, 95% CI 0.54 [-0.32, 1.40] 0.54 [-0.31, 1.40]	Chronic Viral Hepatitis Healthy Control Std. Mean Difference N. Fixed, 95% Cl Chronic Viral Hepatitis Healthy Control Std. Mean Difference N. Fixed, 95% Cl
Heterogeneity. ChP = Test for overall effect D. PD-1 Study or Subgroup Boeijen, 2017 Yong, 2018 Total (95% Cl) Heterogeneity. ChP = Test for overall effect E. TIM-3 Study or Subgroup Boeijen, 2017 Yong, 2018	5.30, df = 3 Z = 6.86 (P Chronii <u>Mean</u> 17.7904 27.98 1.24, df = 1 Z = 2.42 (P Chronii <u>Mean</u> 1.828996 39.40476	(P = 0.15); P < 0.00001) c Viral Heps <u>SD</u> 12.50488 14.42 (P = 0.27); P = 0.02) c Viral Heps <u>SD</u> 3.286539 10.57784	atitis <u>Total</u> 10 21 31 31 31 31 31 31 31 31 31 31 31 31 31	Heat Mean 14.43603 15.25 Heat Mean 0.570012 34.05093	thy Contro <u>SD</u> 6.390273 8.73 thy Contro <u>SD</u> 0.585821 5.024782	59 12 12 24 24 <u>Total</u> 12 12	S Weight 44.2% 55.8% 100.0% Weight 41.7% 58.3%	I.42 [1.02, 1.03] Rd. Mean Difference IV. Fixed, 95% CI 0.33 [-0.51, 1.18] 0.98 [0.23, 1.73] 0.69 [0.13, 1.26] Std. Mean Difference IV. Fixed, 95% CI 0.54 [-0.32, 1.40] 0.58 [0.14, 1.30]	Chronic Viral Hepatitis Healthy Control Std. Mean Difference N. Fixed, 95% Cl Chronic Viral Hepatitis Healthy Control Std. Mean Difference N. Fixed, 95% Cl
Heterogeneity. ChP = Test for overall effect D. PD-1 Study or Subgroup Boeijen, 2017 Yong, 2018 Total (95% CI) Heterogeneity. ChP = Test for overall effect E. TIM-3 Study or Subgroup Boeijen, 2017 Yong, 2018 Total (95% CI)	5.30, df = 3 Z = 6.86 (P Chronii <u>Mean</u> 17.7904 27.98 1.24, df = 1 Z = 2.42 (P Chronii <u>Mean</u> 1.828896 39.40476	(P = 0.15); P < 0.00001) c Viral Heps SD 12.50488 14.42 (P = 0.27); P = 0.02) c Viral Heps SD 3.286539 10.57784	atitis <u>Total</u> 10 21 31 31 31 31 31 31 19% atitis <u>Total</u> 10 21 31 31 31 31 31 31 31 31 31 3	Heal <u>Mean</u> 14.43603 15.25 Heal <u>Mean</u> 0.570012 34.05093	thy Contro SD 6.390273 8.73 thy Contro SD 0.585821 5.024782	59 17 <u>total</u> 12 12 12 24 24 12 12 12 12 24	S Weight 44.2% 55.8% 100.0% Weight 41.7% 58.3% 100.0%	Nd. Mean Difference IV. Fixed, 95% CI 0.33 [-0.51, 1.18] 0.98 [0.23, 1.73] 0.69 [0.13, 1.26] Std. Mean Difference IV. Fixed, 95% CI 0.54 [-0.32, 1.40] 0.58 [-0.14, 1.30] 0.56 [0.01, 1.12]	Chronic Viral Hepatitis Healthy Control Std. Mean Difference M. Fixed, 95% Cl Chronic Viral Hepatitis Healthy Control Std. Mean Difference N. Fixed, 95% Cl Std. Mean Difference N. Fixed, 95% Cl
Heterogeneity. ChP = Test for overall effect D. PD-1 Study or Subgroup Boeijen, 2017 Yong, 2018 Total (95% Cl) Heterogeneity. ChP = Test for overall effect E. TIM-3 Study or Subgroup Boeijen, 2017 Yong, 2018 Total (95% Cl) Heterogeneity. ChP =	5.30, df = 3 Z = 6.86 (P Chronii <u>Mean</u> 17.7904 27.98 1.24, df = 1 Z = 2.42 (P Chronii <u>Mean</u> 1.828996 39.40476 0.01, df = 1	(P = 0.15); P < 0.00001) c Viral Hepa 12.50488 14.42 (P = 0.27); P = 0.02) c Viral Hepa 3.286539 10.57784 (P = 0.94); P	atitis <u>Total</u> 10 21 31 = 19% atitis <u>Total</u> 10 21 31 = 0%	Heal <u>Mean</u> 14.43603 15.25 Heal <u>Mean</u> 0.570012 34.05093	thy Contro SD 6.390273 8.73 thy Contro <u>SD</u> 0.585821 5.024782	59 Total 12 12 24 24 Total 12 12 12 12 24	S Weight 44.2% 55.8% 100.0% Weight 41.7% 58.3% 100.0%	Xd. Mean Difference IV. Fixed, 95% CI 0.33 [-0.51, 1.18] 0.98 [0.23, 1.73] 0.69 [0.13, 1.26] Std. Mean Difference IV. Fixed, 95% CI 0.54 [-0.32, 1.40] 0.55 [-0.14, 1.30] 0.56 [0.01, 1.12]	Chronic Viral Hepatitis Healthy Control Std. Mean Difference W. Fixed, 95% Cl Chronic Viral Hepatitis Healthy Control Std. Mean Difference N. Fixed, 95% Cl Std. Mean Difference N. Fixed, 95% Cl
Heterogeneily. ChP = Test for overall effect D. PD-1 Study or Subgroup Boeijen, 2017 Yong, 2018 Total (95% Cl) Heterogeneily. ChP = Test for overall effect E. TIM-3 Study or Subgroup Boeijen, 2017 Yong, 2018 Total (95% Cl) Heterogeneily. ChP = Test for overall effect	5.30, df = 3 Z = 6.86 (P Chronii <u>Mean</u> 17.7904 27.98 1.24, df = 1 Z = 2.42 (P Chronii <u>Mean</u> 1.828996 1.828996 1.828996 0.01, df = 1 Z = 1.99 (P	(P = 0.15); P < 0.00001) c Viral Hepa 12.50488 14.42 (P = 0.27); P = 0.02) c Viral Hepa 3.286539 10.57784 (P = 0.94); P = 0.05)	atitis <u>Total</u> 10 21 31 = 19% <u>Total</u> 10 21 10 21 31 = 0%	Heal <u>Mean</u> 14.43603 15.25 Heal <u>Mean</u> 0.570012 34.05093	thy Contro SD 6.390273 8.73 thy Contro SD 0.585821 5.024782	59 Total 12 12 24 24 <u>Total</u> 12 12 12 22	S Weight 44.2% 55.8% 100.0% Weight 41.7% 58.3% 100.0%	Xd. Mean Difference IV. Fixed, 95% CI 0.33 [-0.51, 1.18] 0.98 [0.23, 1.73] 0.69 [0.13, 1.26] Std. Mean Difference IV. Fixed, 95% CI 0.54 [-0.32, 1.40] 0.58 [-0.14, 1.30] 0.56 [0.01, 1.12]	Chronic Viral Hepatitis Healthy Control
Heterogeneily. ChP = Test for overall effect D. PD-1 Study or Subgroup Boeijen, 2017 Yong, 2018 Total (95% Cl) Heterogeneily. ChP = Test for overall effect E. TIM-3 Study or Subgroup Boeijen, 2017 Yong, 2018 Total (95% Cl) Heterogeneily. ChP = Test for overall effect	5.30, df = 3 Z = 6.86 (P Chronii <u>Mean</u> 17.7904 27.98 1.24, df = 1 Z = 2.42 (P Chronii <u>Mean</u> 1.828996 1.828996 1.828996 0.01, df = 1 Z = 1.99 (P	(P = 0.15); P < 0.00001) c Viral Hepa 12.50488 14.42 (P = 0.27); P = 0.02) c Viral Hepa 3.286539 10.57784 (P = 0.94); P = 0.05)	65 57 57 57 57 57 57 57 57 57 5	Heal <u>Mean</u> 14.43603 15.25 Heal <u>Mean</u> 0.570012 34.05093	thy Contro SD 6.390273 8.73 thy Contro <u>SD</u> 0.585821 5.024782	59 Total 12 12 12 24 24 12 12 12 12 24	S Weight 44.2% 55.8% 100.0% Weight 41.7% 58.3% 100.0%	Xd. Mean Difference IV. Fixed, 95% CI 0.33 [-0.51, 1.18] 0.98 [0.23, 1.73] 0.69 [0.13, 1.26] Std. Mean Difference IV. Fixed, 95% CI 0.54 [-0.32, 1.40] 0.58 [-0.14, 1.30] 0.56 [0.01, 1.12]	Chronic Viral Hepatitis Healthy Control Std. Mean Difference W. Fixed, 95% Cl Chronic Viral Hepatitis Healthy Control Std. Mean Difference N. Fixed, 95% Cl Chronic Viral Hepatitis Healthy Control Chronic Viral Hepatitis Healthy Control
Heterogeneity. ChP = Test for overall effect D. PD-1 Study or Subgroup Boeijen, 2017 Yong, 2018 Total (95% CI) Heterogeneity. ChP = Test for overall effect E. TIM-3 Study or Subgroup Boeijen, 2017 Yong, 2018 Total (95% CI) Heterogeneity. ChP = Test for overall effect F. CTLA-4	5.30, df = 3 Z = 6.86 (P Chronii <u>Mean</u> 17.7904 27.98 1.24, df = 1 Z = 2.42 (P Chronii <u>Mean</u> 1.828996 39.40476 0.01, df = 1 Z = 1.99 (P	(P = 0.15); P < 0.00001) c Viral Hepa 12.50488 14.42 (P = 0.27); P = 0.02) c Viral Hepa 3.286539 10.57784 (P = 0.94); P = 0.05) c Viral Hepa	65 65 65 65 65 65 65 65 65 65	Heal Mean 14.43603 15.25 Heal Mean 0.570012 34.05093	thy Contro SD 6.390273 8.73 thy Contro <u>SD</u> 0.585821 5.024782	59 10 12 12 12 24 24 12 12 12 12 12 24	S Weight 44.2% 55.8% 100.0% Weight 41.7% 58.3% 100.0%	Xd. Mean Difference IV. Fixed, 95% CI 0.33 [0.51, 1.18] 0.98 [0.23, 1.73] 0.69 [0.13, 1.26] Std. Mean Difference IV. Fixed, 95% CI 0.54 [0.32, 1.40] 0.58 [0.14, 1.30] 0.56 [0.01, 1.12]	Chronic Viral Hepatitis Healthy Control Std. Mean Difference W. Fixed, 95% Cl Chronic Viral Hepatitis Healthy Control Std. Mean Difference N. Fixed, 95% Cl Chronic Viral Hepatitis Healthy Control Std. Mean Difference Std. Mean Difference
Heterogeneily. ChP = Test for overall effect D. PD-1 Study or Subgroup Boeijen, 2017 Yong, 2018 Total (95% CI) Heterogeneily. ChP = Test for overall effect E. TIM-3 Study or Subgroup Boeijen, 2017 Yong, 2018 Total (95% CI) Heterogeneily. ChP = Test for overall effect F. CTLA-4 Study or Subgroup	5.30, df = 3 Z = 6.86 (P Chronii <u>Mean</u> 17.7904 27.98 1.24, df = 1 Z = 2.42 (P Chronii <u>Mean</u> 1.828996 39.40476 0.01, df = 1 Z = 1.99 (P	(P = 0.15); P < 0.00001) c Viral Hepa <u>SD</u> 12.50488 14.42 (P = 0.27); P = 0.02) c Viral Hepa <u>SD</u> 3.286539 10.57784 (P = 0.94); P = 0.05) c Viral Hepa <u>SD</u>	65 67 67 67 67 67 67 67 67 67 67	Heal Mean 14.43603 15.25 Heal Mean 0.570012 34.05093 Heal Mean	thy Contro <u>SD</u> 6.390273 8.73 thy Contro <u>SD</u> 0.585821 5.024782 thy Contro <u>SD</u>	59 Total 12 12 24 12 24 12 12 12 12 12 24	S Weight 44.2% 55.8% 100.0% Weight 100.0% Weight	Nd. Mean Difference N. Fixed, 95% Cl 0.33 [-0.51, 1.18] 0.98 [0.23, 1.73] 0.69 [0.13, 1.26] Std. Mean Difference N. Fixed, 95% Cl 0.54 [-0.32, 1.40] 0.58 [-0.14, 1.30] 0.56 [0.01, 1.12] N. Fixed, 95% Cl	Chronic Viral Hepatitis Healthy Control Std. Mean Difference N. Fixed, 95% Cl Chronic Viral Hepatitis Healthy Control Std. Mean Difference N. Fixed, 95% Cl Chronic Viral Hepatitis Healthy Control Std. Mean Difference N. Fixed, 95% Cl Std. Mean Difference N. Fi
Heterogeneily. ChP = Test for overall effect D. PD-1 Study or Subgroup Boeijen, 2017 Yong, 2018 Total (95% Cl) Heterogeneily. ChP = Test for overall effect E. TIM-3 Study or Subgroup Boeijen, 2017 Yong, 2018 Total (95% Cl) Heterogeneily. ChP = Test for overall effect F. CTLA-4 Study or Subgroup Boeijen, 2017	5.30, df = 3 Z = 6.86 (P Chronii <u>Mean</u> 17.7904 27.98 1.24, df = 1 Z = 2.42 (P Chronii <u>Mean</u> 1.828996 39.40476 0.01, df = 1 Z = 1.99 (P Chronii <u>Mean</u> 1.626478	(P = 0.15); P < 0.00001) c Viral Heps SD 12.50488 14.42 (P = 0.27); P = 0.02) c Viral Heps SD 3.286539 10.57784 (P = 0.94); P = 0.05) c Viral Heps SD 1.55142	05 05 atitis Total 10 21 31 = 19% atitis Total 10 21 31 = 0% atitis Total 11 = 0% atitis Total 10 10 21 31 31 = 0%	Heat Mean 14.43603 15.25 Heat Mean 0.570012 34.05093 Heat Mean 0.825193	thy Contro <u>SD</u> 6.390273 8.73 thy Contro <u>SD</u> 0.585821 5.024782 thy Contro <u>SD</u> 0.542394	59 Total 12 12 12 24 24 12 24 12 24 24	S Weight 44.2% 55.8% 100.0% Weight 41.7% 58.3% 100.0% Weight 42.9%	Nd: Mean Difference IV. Fixed, 95% CI 0.33 [-0.51, 1.18] 0.98 [0.23, 1.73] 0.69 [0.13, 1.26] Std. Mean Difference IV. Fixed, 95% CI 0.54 [-0.32, 1.40] 0.58 [0.14, 1.30] 0.56 [0.01, 1.12] IV. Fixed, 95% CI 0.68 [-0.18, 1.58]	Chronic Viral Hepatitis Healthy Control Std. Mean Difference N. Fixed, 95% Cl Chronic Viral Hepatitis Healthy Control Std. Mean Difference N. Fixed, 95% Cl Chronic Viral Hepatitis Healthy Control Std. Mean Difference N. Fixed, 95% Cl Std. Mean Difference N. Fixed, 95% Cl Std. Mean Difference
PL-1 Study or Subgroup Boeijen, 2017 Yong, 2018 Test for overall effect Beeijen, 2017 Yong, 2018 Total (95% CI) Heterogeneity. ChP= Test for overall effect E. TIM-3 Study or Subgroup Boeijen, 2017 Yong, 2018 Total (95% CI) Heterogeneity. ChP= Test for overall effect F. CTLA-4 Study or Subgroup Boeijen, 2017 Yong, 2018	5.30, df = 3 Z = 6.86 (P Chronii <u>Mean</u> 17.7904 27.98 1.24, df = 1 Z = 2.42 (P Chronii <u>Mean</u> 1.828996 39.40476 0.01, df = 1 Z = 1.99 (P Chronii <u>Mean</u> 1.626478 5.083608	(P = 0.15); P < 0.00001) c Viral Heps SD 12.50488 14.42 (P = 0.27); P = 0.02) c Viral Heps c Viral Heps c Viral Heps 1.55142 3.554843	05 05 atitis Total 10 21 31 10 21 31 10 21 31 10 21 31 10 21 31 10 21 31 10 21 31 10 21 31 31 31 31 10 10 10 21 10	Heal <u>Mean</u> 14.43603 15.25 Heal <u>Mean</u> 0.570012 34.05093 Heal <u>Mean</u> 0.825193 1.605758	thy Contro SD 6.390273 8.73 8.73 thy Contro SD 0.585821 5.024782 thy Contro SD 0.542394 1.030754	55 10 12 12 12 24 12 12 12 12 12 12 12 12 12 12	S Weight 44.2% 55.8% 100.0% Weight 41.7% 58.3% 100.0% Weight 42.9% 57.1%	Nd. Mean Difference IV. Fixed, 95% CI 0.33 [-0.51, 1.18] 0.98 [0.23, 1.73] 0.69 [0.13, 1.26] Std. Mean Difference IV. Fixed, 95% CI 0.54 [-0.32, 1.40] 0.58 [-0.14, 1.30] 0.56 [0.01, 1.12] IV. Fixed, 95% CI 0.68 [-0.18, 1.56] 1.18 [0.43, 1.93]	Chronic Viral Hepatitis Healthy Control Std. Mean Difference N. Fixed, 95% Cl Chronic Viral Hepatitis Healthy Control Std. Mean Difference N. Fixed, 95% Cl Chronic Viral Hepatitis Healthy Control Std. Mean Difference N. Fixed, 95% Cl Std. Mean Difference N. Fixed, 95% Cl
Test for overall effect D. PD-1 Study or Subgroup Boeijen, 2017 Yong, 2018 Total (95% CI) Heterogeneity: ChP= Test for overall effect E. TIM-3 Study or Subgroup Boeijen, 2017 Yong, 2018 Total (95% CI) Heterogeneity: ChP= Test for overall effect F. CTLA-4 Study or Subgroup Boeijen, 2017 Yong, 2018 Total (95% CI)	5.30, df = 3 Z = 6.86 (P Chronii <u>Mean</u> 17.7904 27.98 1.24, df = 1 Z = 2.42 (P Chronii <u>Mean</u> 1.828996 39.40476 0.01, df = 1 Z = 1.99 (P Chronii <u>Mean</u> 1.626478 5.083608	(P = 0.15); P < 0.00001) c Viral Hepz SD 12.50488 14.42 (P = 0.27); P = 0.02) c Viral Hepz SD 1.55142 3.554843	65 65 65 65 65 65 65 65 65 65	Heal <u>Mean</u> 14.43603 15.25 Heal <u>Mean</u> 0.825193 1.605758	thy Contro SD 6.390273 8.73 thy Contro SD 0.585821 5.024782 thy Contro SD 0.542394 1.030754	59 10 11 12 12 12 24 12 12 12 12 12 12 12 12 12 12	S Weight 44.2% 55.8% 100.0% Weight 41.7% 58.3% 100.0% Weight 42.9% 57.1%	Nd. Mean Difference IV. Fixed, 95% CI 0.33 [-0.51, 1.18] 0.98 [0.23, 1.73] 0.69 [0.13, 1.26] Std. Mean Difference IV. Fixed, 95% CI 0.54 [-0.32, 1.40] 0.58 [-0.14, 1.30] 0.56 [0.01, 1.12] IV. Fixed, 95% CI 0.56 [0.01, 1.12] IV. Fixed, 95% CI 0.69 [-0.18, 1.56] 1.18 [0.43, 1.93] 0.97 [0.40, 1.54]	Chronic Viral Hepatitis Healthy Control Std. Mean Difference M. Fixed, 95% Cl Chronic Viral Hepatitis Healthy Control Std. Mean Difference N. Fixed, 95% Cl Chronic Viral Hepatitis Healthy Control Std. Mean Difference N. Fixed, 95% Cl Std. Mean Difference N. Fi
Heterogeneily. ChP = Test for overall effect D. PD-1 Study or Subgroup Boeijen, 2017 Yong, 2018 Total (95% CI) Heterogeneily. ChP = Test for overall effect E. TIM-3 Study or Subgroup Boeijen, 2017 Yong, 2018 Total (95% CI) Heterogeneily. ChP = Test for overall effect E. CTLA-4 Study or Subgroup Boeijen, 2017 Yong, 2018 Total (95% CI) Heterogeneily. ChP =	5.30, df = 3 Z = 6.86 (P Chronii <u>Mean</u> 17.7904 27.98 1.24, df = 1 Z = 2.42 (P Chronii <u>Mean</u> 1.828996 39.40476 0.01, df = 1 Z = 1.99 (P Chronii <u>Mean</u> 1.626478 5.083608 0.69, df = 1	(P = 0.15); P < 0.00001) c Viral Hepa <u>SD</u> 12.50488 14.42 (P = 0.27); P = 0.02) c Viral Hepa <u>3.286539</u> 10.57784 (P = 0.94); P = 0.05) c Viral Hepa <u>SD</u> 1.55142 3.554843 (P = 0.41); P	05 05 atitis Total 10 21 31 31	Heal <u>Mean</u> 14.43603 15.25 Heal <u>Mean</u> 0.870012 34.05093 Heal <u>Mean</u> 0.825193 1.605758	thy Contro <u>SD</u> 6.390273 8.73 thy Contro <u>SD</u> 0.585821 5.024782 thy Contro <u>SD</u> 0.542394 1.030754	59 Total 12 12 12 24 12 24 12 24 12 12 24 12 12 12 12 12 12 12 12 12 12	S Weight 44.2% 55.8% 100.0% Weight 41.7% 58.3% 100.0% Weight 42.9% 57.1% 100.0%	Nd2 [1.02, 1.03] Nd. Mean Difference W. Fixed, 95% CI 0.33 [0.51, 1.18] 0.98 [0.23, 1.73] 0.69 [0.13, 1.26] Std. Mean Difference W. Fixed, 95% CI 0.54 [0.32, 1.40] 0.58 [0.01, 1.12] 0.56 [0.01, 1.12] W. Fixed, 95% CI 0.56 [0.01, 1.12] 0.56 [0.01, 1.13] 0.56 [0.01, 1.14] 0.56 [0.01, 1.12] 0.56 [0.01, 1.12]	Chronic Viral Hepatitis Healthy Control Std. Mean Difference W. Fixed, 95% Cl Chronic Viral Hepatitis Healthy Control Std. Mean Difference N. Fixed, 95% Cl Chronic Viral Hepatitis Healthy Control Std. Mean Difference N. Fixed, 95% Cl Std. Mean Difference N. Fi
Heterogeneily: ChP = Testfor overall effect D. PD-1 Study or Subgroup Boeijen, 2017 Yong, 2018 Total (95% CI) Heterogeneily: ChP = Testfor overall effect E. TIM-3 Study or Subgroup Boeijen, 2017 Yong, 2018 Total (95% CI) Heterogeneily: ChP = Testfor overall effect E. CTLA-4 Study or Subgroup Boeijen, 2017 Yong, 2018 Total (95% CI) Heterogeneily: ChP = Testfor overall effect	5.30, df = 3 Z = 6.86 (P Chronii <u>Mean</u> 17.7904 27.98 1.24, df = 1 Z = 2.42 (P Chronii <u>Mean</u> 1.828996 39.40476 0.01, df = 1 Z = 1.99 (P Chronii <u>Mean</u> 1.626478 5.083608 0.69, df = 1 Z = 3.34 (P	(P = 0.15); P < 0.00001) c Viral Hepa <u>SD</u> 12.50488 14.42 (P = 0.27); P = 0.02) c Viral Hepa <u>SD</u> 3.286539 10.57784 (P = 0.94); P = 0.05) c Viral Hepa <u>SD</u> 1.55142 3.554843 (P = 0.41); P = 0.0008)	05 05 atitis Total 10 21 31 = 19% atitis Total 10 21 31 = 19% atitis Total 10 21 31 = 0% atitis Total 10 21 31 = 0%	Heal <u>Mean</u> 14.43603 15.25 Heal <u>Mean</u> 0.570012 34.05093 Heal <u>Mean</u> 0.825193 1.605758	thy Contro <u>SD</u> 6.390273 8.73 thy Contro <u>SD</u> 0.585821 5.024782 thy Contro <u>SD</u> 0.542394 1.030754	59 Total 12 12 12 24 Total 12 24 12 12 24 12 12 12 12 12 12 12 12 12 12	S Weight 44.2% 55.8% 100.0% Weight 41.7% 58.3% 100.0% Weight 42.9% 57.1% 100.0%	Nd: Mean Difference N. Fixed, 95% CI 0.33 [-0.51, 1.18] 0.96 [0.23, 1.73] 0.69 [0.13, 1.26] Std. Mean Difference N. Fixed, 95% CI 0.54 [-0.32, 1.40] 0.58 [-0.14, 1.30] 0.56 [0.01, 1.12] N. Fixed, 95% CI 0.56 [0.01, 1.12] N. Fixed, 95% CI 0.69 [-0.18, 1.56] 1.18 [0.43, 1.93] 0.97 [0.40, 1.54]	Chronic Viral Hepatitis Healthy Control Std. Mean Difference N. Fixed, 95% Cl Chronic Viral Hepatitis Healthy Control Std. Mean Difference N. Fixed, 95% Cl Chronic Viral Hepatitis Healthy Control Std. Mean Difference N. Fixed, 95% Cl Chronic Viral Hepatitis Healthy Control Std. Mean Difference N. Fixed, 95% Cl Chronic Viral Hepatitis Healthy Control Chronic Viral Hepatitis Healthy Control Std. Mean Difference N. Fixed, 95% Cl Chronic Viral Hepatitis Healthy Control

Figure 3. Phenotype of peripheral MAIT cells is shown.

influenza virus, and HCV-exposed dendritic cells (DCs) or macrophages could activate MAIT cells (33). Moreover, stimulating MAIT cells with anti-CD3/CD28 double beads (28, 40), mitogenic phorbol myristate acetate (PMA)/Ionomycin (24, 27, 41-43), *E. coli* (24, 30, 44) or cytokines such as IL-12 and IL-18 (12, 26, 30, 42, 44), are usually used in function assay. In our five included studies for function assay, three articles applied IL-12/IL-18 stimulation, one applied double beads, and one applied IL-12/IL-18/E.coli, which may partly influent the results of the meta-analysis.

There are several limitations to this study. First, only a few studies were included, and the size of the included studies was small. Second, the authors' silences to email replies prevented us from collecting original data; as a result, the software GetData Graph Digitizer 2.22 was used to get data from the articles. Third, there was not enough

. IFN-γ									
	Chronic	: Viral Hepa	titis	Heal	thy Contro			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% Cl	IV, Fixed, 95% Cl
Beudeker, 2018	32.1	11.23388	7	28.40889	26.11284	9	10.6%	0.17 [-0.82, 1.16]	
Boeijen, 2017	26.90011	14.67452	15	28.41751	14.60395	14	19.5%	-0.10 [-0.83, 0.63]	
Dias, 2019	37.13913	16.40198	17	40.93969	10.7355	10	16.9%	-0.25 [-1.04, 0.53]	_ <u>_</u>
Provine, 2018	38.64	16.57	12	38.27	14.47	12	16.2%	0.02 [-0.78, 0.82]	
Spaan, 2016	31.55483	20.37968	27	17.59489	11.67809	12	21.1%	0.75 [0.05, 1.45]	—
Yong, 2018	5.003922	3.623021	15	11.91176	22.25163	10	15.7%	-0.47 [-1.28, 0.34]	
Total (95% CI)			93			67	100.0%	0.04 [-0.28, 0.37]	+
Heterogeneity: Chi ² =	6.18, df = 5	(P = 0.29); I ²	'= 19%						
Test for overall effect:	Z = 0.26 (P	= 0.79)						Chr	onic Viral Hepatitis Healthy Control
. TNF-α	Chronic	Viral Llana	titio	Healt	by Control				014 11
Church and Carls and	Chronic	viral Hepa	uus	riealti	iy Control	× - 4 - 1	10/-1-1-1	Sta. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	iotal	vveight	IV, Random, 95% Cl	IV, Random, 95% CI
Boeijen, 2017	12.1259	3.241843	7	12.27118	5.75693	12	32.5%	-0.03 [-0.96, 0.90]	
Dias, 2019	3.058451	2.068097	17	4.370254	2.02847	10	35.2%	-0.62 [-1.42, 0.18]	
Yong, 2018	6.112423	4.34787	15	18.09626	8.63323	11	32.3%	-1.79 [-2.73, -0.85]	_
			30			33	100.0%	-0.80 [-1.77, 0.16]	
Total (95% CI)			39						
Total (95% CI) Heterogeneity: Tau² =	= 0.52; Chi² =	7.08, df = 2	(P = 0.0	3); I² = 72%					+ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$
Total (95% CI) Heterogeneity: Tau ² = Test for overall effect:	= 0.52; Chi² = : Z = 1.63 (P :	= 7.08, df = 2 = 0.10)	(P = 0.0	3); I² = 72%				Chr	-4 -2 0 2 4 onic Viral Hepatitis Healthy Control
Total (95% CI) Heterogeneity: Tau ² = Test for overall effect:	= 0.52; Chi² = : Z = 1.63 (P :	= 7.08, df = 2 = 0.10)	(P = 0.0	3); I² = 72%				Chr	-4 -2 0 2 4 onic Viral Hepatitis Healthy Control
Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: C. Gr B	= 0.52; Chi ^z = : Z = 1.63 (P :	: 7.08, df = 2 = 0.10)	(P = 0.0	3); I² = 72%				Chr	-1 -1 -1 -1 -4 -2 0 2 4 onic Viral Hepatitis Healthy Control
Total (95% CI) Heterogeneity: Tau² = Test for overall effect: C. Gr B	= 0.52; Chi² = : Z = 1.63 (P : Chronic	: 7.08, df = 2 = 0.10) : Viral Hepa	(P = 0.0	3); I² = 72% Healti	hy Control			Chr Std. Mean Difference	-4 -2 0 2 4 onic Viral Hepatitis Healthy Control Std. Mean Difference
Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: C. Gr B Study or Subgroup	= 0.52; Chi² = : Z = 1.63 (P : Chronic Mean	: 7.08, df = 2 = 0.10) : Viral Hepa SD	(P = 0.0) titis Total	3); I² = 72% Healti Mean	hy Control SD	Total	Weight	Chr Std. Mean Difference IV. Fixed, 95% Cl	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: C. Gr B <u>Study or Subgroup</u> Beudeker, 2018	= 0.52; Chi ² = : Z = 1.63 (P : Chronic <u>Mean</u> 14.6978	7.08, df = 2 = 0.10) Viral Hepa <u>SD</u> 15.57092	titis <u>Total</u> 7	3); I ² = 72% Health <u>Mean</u> 21.15383	hy Control SD 29.16225	<u>Total</u> 9	Weight 19.3%	Chr Std. Mean Difference IV. Fixed, 95% CI -0.25 (-1.24, 0.74)	Std. Mean Difference
Total (95% CI) Heterogeneity: Tau ² = Test for overall effect C. Gr B Study or Subgroup Beudeker, 2018 Boeijen, 2017	= 0.52; Chi ² = Z = 1.63 (P = Chronic Mean 14.6978 35.91283	: 7.08, df = 2 = 0.10) : Viral Hepa <u>SD</u> 15.57092 18.48573	titis <u>Total</u> 7	3); ² = 72% Health <u>Mean</u> 21.15383 25.44635	hy Control SD 29.16225 13.24295	Total 9 12	Weight 19.3% 20.6%	Chr Std. Mean Difference IV. Fixed, 95% CI -0.25 [-1.24, 0.74] 0.65 [-0.31, 1.61]	-4 -2 0 2 4 onic Viral Hepatitis Healthy Control Std. Mean Difference IV, Fixed, 95% Cl
Total (95% CI) Heterogeneity: Tau ² = Test for overall effect Gr B <u>Study or Subgroup</u> Beudeker, 2018 Boeijen, 2017 Dias, 2019	= 0.52; Chi ² = Z = 1.63 (P = Chronic Mean 14.6978 35.91283 2.747579	7.08, df = 2 = 0.10) Viral Hepa 50 15.57092 18.48573 1.638947	titis <u>Total</u> 7 7	3); ² = 72% Health <u>Mean</u> 21.15383 25.44635 3.968355	hy Control SD 29.16225 13.24295 2.385795	<u>Total</u> 9 12 10	Weight 19.3% 20.6% 29.7%	Chr Std. Mean Difference IV, Fixed, 95% CI -0.25 [-1.24, 0.74] 0.65 [-0.31, 1.61] -0.61 [-1.41, 0.19]	-4 -2 0 2 4 onic Viral Hepatitis Healthy Control Std. Mean Difference IV. Fixed, 95% Cl
Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: Gr B <u>Study or Subgroup</u> Beudeker, 2018 Boeijen, 2017 Dias, 2019 Yong, 2018	= 0.52; Chi ² = Z = 1.63 (P = Chronic Mean 14.6978 35.91283 2.747579 34.69387	7.08, df = 2 = 0.10) viral Hepa 50 15.57092 18.48573 1.638947 25.90627	titis <u>Total</u> 7 17 14	3); I ² = 72% Health <u>Mean</u> 21.15383 25.44635 3.968355 38.75983	by Control SD 29.16225 13.24295 2.385795 25.52468	<u>Total</u> 9 12 10 11	Weight 19.3% 20.6% 29.7% 30.4%	Chr Std. Mean Difference <u>IV. Fixed, 95% CI</u> -0.25 [-1.24, 0.74] 0.65 [-0.31, 1.61] -0.61 [-1.41, 0.19] -0.15 [-0.94, 0.64]	-4 -2 0 2 4 onic Viral Hepatitis Healthy Control Std. Mean Difference IV. Fixed, 95% Cl
Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: C. Gr B <u>Study or Subgroup</u> Beudeker, 2018 Boeijen, 2019 Yong, 2018 Total (95% CI)	= 0.52; Chi ² = Z = 1.63 (P Chronic <u>Mean</u> 14.6978 35.91283 2.747579 34.69387	7.08, df = 2 = 0.10) : Viral Hepa 5D 15.57092 18.48573 1.638947 25.90627	titis <u>Total</u> 7 17 14 45	3); I ² = 72% Health <u>Mean</u> 21.15383 25.44635 3.968355 38.75983	by Control SD 29.16225 13.24295 2.385795 25.52468	<u>Total</u> 9 12 10 11	Weight 19.3% 20.6% 29.7% 30.4%	Chr Std. Mean Difference IV, Fixed, 95% CI -0.25 [-1.24, 0.74] -0.61 [-1.41, 0.19] -0.15 [-0.94, 0.64] -0.14 [-0.58, 0.29]	-4 -2 0 2 4 onic Viral Hepatitis Healthy Control Std. Mean Difference IV. Fixed, 95% Cl
Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: C. Gr B Study or Subgroup Beudeker, 2018 Boeijen, 2019 Dias, 2019 Yong, 2018 Total (95% CI) Heterogeneity: Chi ² =	= 0.52; Chi ² = Z = 1.63 (P = Chronic Mean 14.6978 35.91283 2.747579 34.69387 = 3.99, df = 3	: 7.08, df = 2 = 0.10) : Viral Hepa 50 15.57092 18.48573 1.638947 25.90627 (P = 0.26); l ²	titis Total 7 17 14 45 r = 25%	3); I ² = 72% Health <u>Mean</u> 21.15383 25.44635 3.968355 38.75983	by Control SD 29.16225 13.24295 2.385795 25.52468	Total 9 12 10 11 42	Weight 19.3% 20.6% 29.7% 30.4% 100.0%	Chr Std. Mean Difference IV. Fixed, 95% CI -0.25 [-1.24, 0.74] 0.65 [-0.31, 1.61] -0.61 [-1.41, 0.19] -0.15 [-0.94, 0.64] -0.14 [-0.58, 0.29]	Std. Mean Difference IV. Fixed, 95% CI
Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: C. Gr B <u>Study or Subgroup</u> Beudeker, 2018 Boeijen, 2019 Yong, 2018 Total (95% CI) Heterogeneity: Chi ² = Test for overall effect:	= 0.52; Chi ^a = Z = 1.63 (P = Chronic Mean 14.6978 35.91283 2.747579 34.69387 : 3.99, df = 3 : Z = 0.63 (P =	<pre>: 7.08, df = 2 = 0.10) : Viral Hepa 50 15.57092 18.48573 1.638947 25.90627 (P = 0.26); P = 0.53)</pre>	titis Total 7 17 14 45 2 = 25%	3); I ² = 72% Health <u>Mean</u> 21.15383 25.44635 3.968355 38.75983	hy Control SD 29.16225 13.24295 2.385795 25.52468	<u>Total</u> 9 12 10 11 42	Weight 19.3% 20.6% 29.7% 30.4% 100.0%	Chr Std. Mean Difference IV. Fixed, 95% CI -0.25 [-1.24, 0.74] 0.65 [-0.31, 1.61] -0.61 [-1.41, 0.19] -0.15 [-0.94, 0.64] -0.14 [-0.58, 0.29] Chr	Std. Mean Difference IV. Fixed, 95% CI
Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: C. Gr B <u>Study or Subgroup</u> Beudeker, 2018 Boeijen, 2017 Dias, 2019 Yong, 2018 Total (95% CI) Heterogeneity: Chi ² = Test for overall effect:	= 0.52; Chi ² = Z = 1.63 (P = <u>Mean</u> 14.6978 35.91283 2.747579 34.69387 • 3.99, df = 3 Z = 0.63 (P =	7.08, df = 2 = 0.10) : Viral Hepa <u>SD</u> 15.57092 18.48573 1.638947 25.90627 (P = 0.26); P = 0.53)	titis <u>Total</u> 7 17 14 45 2= 25%	Healti <u>Mean</u> 21.15383 25.44635 3.968355 38.75983	hy Control 29.16225 13.24295 2.385795 25.52468	Total 9 12 10 11 42	Weight 19.3% 20.6% 29.7% 30.4% 100.0%	Chr Std. Mean Difference IV. Fixed, 95% CI -0.25 [-1.24, 0.74] 0.65 [-0.31, 1.61] -0.61 [-1.41, 0.19] -0.15 [-0.94, 0.64] -0.14 [-0.58, 0.29] Chr	Std. Mean Difference IV. Fixed, 95% CI
Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: C. Gr B Study or Subgroup Beudeker, 2018 Boeijen, 2018 Dias, 2019 Yong, 2018 Total (95% CI) Heterogeneity: Chi ² = Test for overall effect: D. Perforin	2 0.52; Chi ² = Z = 1.63 (P = <u>Mean</u> 14.6978 35.91283 2.747579 34.69387 3.469387 3.99, df = 3 Z = 0.63 (P =	7.08, df = 2 = 0.10) :: Viral Hepa <u>SD</u> 15.57092 18.48573 1.638947 25.90627 (P = 0.26); P = 0.53)	titis <u>Total</u> 7 17 14 45 2 = 25%	Health Mean 21.15383 25.44635 3.968355 38.75983	hy Control SD 29.16225 13.24295 2.385795 25.52468	<u>Total</u> 9 12 10 11 42	Weight 19.3% 20.6% 29.7% 30.4% 100.0%	Chr Std. Mean Difference <u>IV. Fixed, 95% CI</u> -0.25 [-1.24, 0.74] 0.65 [-0.31, 1.61] -0.61 [-1.41, 0.19] -0.15 [-0.94, 0.64] -0.14 [-0.58, 0.29] Chr	Std. Mean Difference N. Fixed, 95% CI -2 -1 0 1 2 onic Viral Hepatitis Healthy Control
Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: C. Gr B Study or Subgroup Beudeker, 2018 Boeijen, 2017 Dias, 2019 Yong, 2018 Total (95% CI) Heterogeneity: Chi ² = Test for overall effect: D. Perforin	 0.52; Chi² = Z = 1.63 (P = Z = 1.63 (P = Mean 14.6978 35.9128) 3.69233 (2.747579 34.69387 34.69387 3.99, df = 3 Z = 0.63 (P = Chronic 	7.08, df = 2 = 0.10) :: Viral Hepa 50 15.57092 18.48573 1.638947 25.90627 (P = 0.26); P = 0.53) :: Viral Hepa	titis <u>Total</u> 7 7 17 14 45 2= 25%	3); I ² = 72% Health <u>Mean</u> 21.15383 25.44635 3.968355 38.75983 Health	ny Control SD 29.16225 13.24295 2.385795 25.52468	<u>Total</u> 9 12 10 11 42	Weightt 19.3% 20.6% 29.7% 30.4% 100.0%	Chr Std. Mean Difference <u>IV. Fixed, 95% CI</u> -0.25 [-1.24, 0.74] 0.65 [-0.31, 1.61] -0.61 [-1.41, 0.19] -0.15 [-0.94, 0.64] -0.14 [-0.58, 0.29] Chr Std. Mean Difference	Std. Mean Difference N, Fixed, 95% Cl -2 -1 0 1 2 onic Viral Hepatitis Healthy Control Std. Mean Difference Std. Mean Difference Std. Mean Difference
Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: C. Gr B <u>Study or Subgroup</u> Beudeker, 2018 Boeijen, 2017 Dias, 2019 Yong, 2018 Total (95% CI) Heterogeneity: Chi ² = Test for overall effect: D. Perforin Study or Subgroup	: 0.52; Chi ² = Z = 1.63 (P : <u>Mean</u> 14.6978 35.9123 2.747579 34.69387 3.999, df = 3 Z = 0.63 (P : <u>Chronic</u> <u>Mean</u>	7.08, df = 2 = 0.10) : Viral Hepa <u>SD</u> 15.57092 18.48573 1.638947 25.90627 (P = 0.26); P = 0.53) : Viral Hepa <u>SD</u>	titis <u>Total</u> 7 7 17 14 45 2 = 25% titis <u>Total</u>	3); I ² = 72% Healti <u>Mean</u> 21.15383 25.44635 3.968355 38.75983 Healti <u>Mean</u>	hy Control SD 29.16225 2.385795 25.52468 hy Control SD	Total 9 12 10 11 42 Total	Weight 19.3% 20.6% 29.7% 30.4% 100.0% Weight	Chr Std. Mean Difference IV. Fixed, 95% CI -0.25 [-1.24, 0.74] 0.65 [-0.31, 1.61] -0.61 [-1.41, 0.19] -0.15 [-0.94, 0.64] -0.14 [-0.58, 0.29] Chr Std. Mean Difference IV. Fixed, 95% CI	Std. Mean Difference V. Fixed, 95% Cl Viral Hepatitis Healthy Control Std. Mean Difference V. Fixed, 95% Cl Std. Mean Difference N. Fixed, 95% Cl
Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: C. Gr B Study or Subgroup Beudeker, 2018 Boeijen, 2018 Dias, 2019 Yong, 2018 Total (95% CI) Heterogeneity: Chi ² = Test for overall effect: Perforin Study or Subgroup 30eijen, 2017	: 0.52; Chi ² = Z = 1.63 (P : <u>Mean</u> 14.6978 35.91283 2.747579 34.69387 3.99, df = 3 Z = 0.63 (P : <u>Mean</u> 3.973064	7.08, df = 2 = 0.10) : Viral Hepa <u>SD</u> 15.57092 18.48573 1.638947 25.90627 (P = 0.26); P = 0.53) : Viral Hepa <u>SD</u> 2.172351	titis Total 7 7 17 14 45 $^2 = 25\%$ titis Total 7	3); I ² = 72% Healti <u>Mean</u> 21.15383 25.44635 3.968355 38.75983 Healti <u>Mean</u> 4.736249	hy Control <u>SD</u> 29.16225 13.24295 2.385795 25.52468 hy Control <u>SD</u> 5.800941	<u>Total</u> 9 12 10 11 42 <u>Total</u> 12	Weightt 19.3% 20.6% 29.7% 30.4% 100.0% Weightt 41.4%	Chr Std. Mean Difference <u>IV. Fixed, 95% CI</u> -0.25 [-1.24, 0.74] 0.65 [-0.31, 1.61] -0.61 [-1.41, 0.19] -0.15 [-0.94, 0.64] -0.14 [-0.58, 0.29] Chr Std. Mean Difference <u>IV. Fixed, 95% CI</u> -0.15 [-1.08, 0.78]	Std. Mean Difference N. Fixed, 95% Cl -2 -1 0 1 2 onic Viral Hepatitis Healthy Control Std. Mean Difference N. Fixed, 95% Cl -2 -1 0 1 2 onic Viral Hepatitis Healthy Control Std. Mean Difference N. Fixed, 95% Cl
Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: C. Gr B <u>Study or Subgroup</u> Beudeker, 2018 Boeijen, 2017 Dias, 2019 Yong, 2018 Total (95% CI) Heterogeneity: Chi ² = Test for overall effect: D. Perforin <u>Study or Subgroup</u> 30eijen, 2017 (ong, 2018	: 0.52; Chi ² = Z = 1.63 (P : <u>Mean</u> 14.6978 35.91283 2.747579 34.69387 3.99, df = 3 Z = 0.63 (P : <u>Chronic</u> <u>Mean</u> 3.973064 21.23407	7.08, df = 2 = 0.10) : Viral Hepa <u>SD</u> 15.57092 18.48573 1.638947 25.90627 (P = 0.26); P = 0.53) : Viral Hepa <u>SD</u> 2.172351 25.53213	tittis <u>Total</u> 7 7 17 14 45 2 = 25% tittis <u>Total</u> 7 14	Health Mean 21.15383 25.44635 3.968355 38.75983 Health Mean 4.736249 29.63234	hy Control 29.16225 13.24295 2.385795 25.52468 hy Control <u>SD</u> 5.800941 18.78464	<u>Total</u> 9 12 10 11 42 <u>Total</u> 12 11	Weightt 19.3% 20.6% 29.7% 30.4% 100.0% Weightt 41.4% 58.6%	Chr Std. Mean Difference IV, Fixed, 95% CI -0.25 [-1.24, 0.74] 0.65 [-0.31, 1.61] -0.61 [-1.41, 0.19] -0.15 [-0.94, 0.64] -0.14 [-0.58, 0.29] Chr Std. Mean Difference IV, Fixed, 95% CI -0.15 [-1.08, 0.78] -0.35 [-1.14, 0.43]	Std. Mean Difference IV. Fixed, 95% Cl -2 -1 0 1 2 onic Viral Hepatitis Healthy Control Std. Mean Difference V. Fixed, 95% Cl Std. Mean Difference IV. Fixed, 95% Cl
Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: C. Gr B Study or Subgroup Beudeker, 2018 Boeijen, 2017 Dias, 2019 Yong, 2018 Total (95% CI) Heterogeneity: Chi ² = Test for overall effect: D. Perforin Study or Subgroup Boeijen, 2017 Yong, 2018 Total (95% CI)	2 0.52; Chi ² = Z = 1.63 (P : <u>Mean</u> 14.6978 35.91283 2.747579 34.69387 3.99, df = 3 Z = 0.63 (P : <u>Chronic Mean</u> 3.973064 21.23407	7.08, df = 2 = 0.10) : Viral Hepa <u>SD</u> 15.57092 18.48573 18.48573 18.48573 18.48573 18.638947 25.90627 (P = 0.26); P = 0.53) : Viral Hepa <u>SD</u> 2.172351 25.53213	tittis <u>Total</u> 7 7 17 14 45 2 = 25% tittis <u>Total</u> 7 15 22	Health Mean 21.15383 25.44635 3.968355 38.75983 Health Mean 4.736249 29.63234	hy Control 29.16225 13.24295 2.385795 25.52468 hy Control <u>SD</u> 5.800941 18.78464	<u>Total</u> 9 12 10 11 42 <u>Total</u> 12 11 23	Weight 19.3% 20.6% 29.7% 30.4% 100.0% Weight 41.4% 58.6% 100.0%	Chr Std. Mean Difference IV, Fixed, 95% CI -0.25 [-1.24, 0.74] 0.65 [-0.31, 1.61] -0.61 [-1.41, 0.19] -0.15 [-0.94, 0.64] -0.14 [-0.58, 0.29] Chr Std. Mean Difference IV, Fixed, 95% CI -0.15 [-1.08, 0.78] -0.35 [-1.14, 0.43] -0.27 [-0.87, 0.33]	Std. Mean Difference IV. Fixed, 95% Cl -2 -1 0 1 2 onic Viral Hepatitis Healthy Control Std. Mean Difference V. Fixed, 95% Cl Std. Mean Difference IV. Fixed, 95% Cl
Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: C. Gr B Study or Subgroup Beudeker, 2018 Boeijen, 2017 Dias, 2019 Yong, 2018 Total (95% CI) Heterogeneity: Chi ² = Study or Subgroup Soeijen, 2017 Yong, 2018 Fotal (95% CI) Heterogeneity: Chi ² =	 0.52; Chi² = Z = 1.63 (P = Z = 1.63 (P =	7.08, df = 2 = 0.10) : Viral Hepa 50 15.57092 18.48573 1.638947 25.90627 (P = 0.26); P = 0.53) : Viral Hepa 50 2.172351 25.53213 P = 0.74) P	titis Total 7 7 17 14 45 25% titis Total 7 5 22 = 0%	Health <u>Mean</u> 21.15383 25.44635 3.968355 38.75983 Health <u>Mean</u> 4.736249 29.63234	hy Control SD 29.16225 13.24295 25.52468 hy Control S00941 18.78464	Total 9 12 10 11 42 <u>Total</u> 12 11 23	Weight 19.3% 20.6% 29.7% 30.4% 100.0% Weight 41.4% 58.6% 100.0%	Chr Std. Mean Difference <u>IV. Fixed, 95% CI</u> -0.25 [-1.24, 0.74] 0.65 [-0.31, 1.61] -0.61 [-1.41, 0.19] -0.15 [-0.94, 0.64] -0.14 [-0.58, 0.29] Chr Std. Mean Difference <u>IV. Fixed, 95% CI</u> -0.15 [-1.08, 0.78] -0.35 [-1.14, 0.43] -0.27 [-0.87, 0.33]	Std. Mean Difference N. Fixed, 95% Cl -2 -1 0 1 2 onic Viral Hepatitis Healthy Control Std. Mean Difference N. Fixed, 95% Cl Std. Mean Difference N. Fixed, 95% Cl
Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: C. Gr B <u>Study or Subgroup</u> Beudeker, 2018 Boeijen, 2017 Dias, 2019 Yong, 2018 Total (95% CI) Heterogeneity: Chi ² = Test for overall effect: D. Perforin <u>Study or Subgroup</u> Boeijen, 2017 fong, 2018 fotal (95% CI) Heterogeneity: Chi ² = t	 0.52; Chi² = Z = 1.63 (P = Z = 1.63 (P = Mean 14.6978 35.91283 2.747579 34.69387 3.99, df = 3 Z = 0.63 (P = Mean 3.973064 21.23407 0.11, df = 1 (Z = 0.88 (P = Mean 3.973064 21.23407) 	7.08, df = 2 = 0.10) : Viral Hepa 50 15.57092 18.48573 1.638947 25.90627 (P = 0.26); P = 0.53) : Viral Hepa 50 2.172351 25.53213 P = 0.74); P 0.38)	tittis Total 7 17 14 45 $^2 = 25\%$ tittis Total 7 15 22 = 0%	Health Mean 21.15383 25.44635 38.75983 Health Mean 4.736249 29.63234	hy Control SD 29.16225 13.24295 2.385795 25.52468 hy Control SD 5.800941 18.78464	<u>Total</u> 9 12 10 11 42 <u>Total</u> 11 23	Weight 19.3% 20.6% 29.7% 30.4% 100.0% Weight 41.4% 58.6% 100.0%	Chr Std. Mean Difference N. Fixed, 95% CI -0.25 [-1.24, 0.74] 0.65 [-0.31, 1.61] -0.61 [-1.41, 0.19] -0.15 [-0.94, 0.64] -0.14 [-0.58, 0.29] Chr Std. Mean Difference N. Fixed, 95% CI -0.15 [-1.08, 0.78] -0.35 [-1.14, 0.43] -0.27 [-0.87, 0.33]	Std. Mean Difference N, Fixed, 95% Cl -2 -1 0 1 2 onic Viral Hepatitis Healthy Control Std. Mean Difference N, Fixed, 95% Cl -2 -1 0 1 2 Std. Mean Difference N, Fixed, 95% Cl -2 -1 0 1 2 onic Viral Hepatitis Healthy Control







study to analyze the intrahepatic MAIT cells and compare MAIT cells before and after the treatment. Therefore, future studies should be conducted to provide insight into the mechanisms of CVH to yield a new and better treatment strategy against CVH.

5.1. Conclusions

Our meta-analysis demonstrates a significant depletion of MAIT cells in the peripheral blood of patients with CVH (hepatitis B and C subgroups) compared to healthy controls. In addition, MAIT cells in patients with CVH displayed an activated and exhausted phenotype, which might result in the reduction of MAIT cells; however, no impairment was observed in cytolytic function and cytokine production of these cells.

Acknowledgments

The authors thank Sandeep Kumar Karn for paper polishing and organizing literature for this review.

Footnotes

Authors' Contribution: Study concept and design: Dazhi Zhang and Qinling Liu; acquisition of data: Qinling Liu, Feng Zhu, and Yujing Shi; analysis and interpretation of data, statistical analysis, and drafting of the manuscript: Qinling Liu and Feng Zhu; critical revision of the manuscript for important intellectual content: Dazhi Zhang; study supervision: Dazhi Zhang.

Conflict of Interests: The authors declare that there is no conflict of interest in this study.

Funding/Support: This research was supported by the National Natural Science Foundation of China (CN) (81171560, 30930082, 81171561, 30972584), the National Science and Technology Major Project of China (2008ZX10002-006, 2012ZX1002007001, 2011ZX09302005, 2012ZX09303001-001, 2012ZX10002003); the National High Technology Research and Development Program of China (2011AA020111), the Key Project of Chongqing Science and Technology Commission (cstc2012ggyyjsB10007), the Chongqing Natural Science Foundation (cstc2011jA10025), and the Medical Research Fund by Chongqing Municipal Health Bureau (2009-1-71).

References

- Shin EC, Sung PS, Park SH. Immune responses and immunopathology in acute and chronic viral hepatitis. *Nat Rev Immunol*. 2016;16(8):509– 23. doi: 10.1038/nri.2016.69. [PubMed: 27374637].
- 2. World Health Organization. *Global Hepatitis Report 2017.* Geneva: World Health Organization; 2017.
- Ringelhan M, McKeating JA, Protzer U. Viral hepatitis and liver cancer. *Philos Trans R Soc Lond B Biol Sci.* 2017;**372**(1732). doi: 10.1098/rstb.2016.0274. [PubMed: 28893941]. [PubMed Central: PMC5597741].
- Porcelli S, Yockey CE, Brenner MB, Balk SP. Analysis of T cell antigen receptor (TCR) expression by human peripheral blood CD4-8alpha/beta T cells demonstrates preferential use of several V beta genes and an invariant TCR alpha chain. J Exp Med. 1993;178(1):1-16. doi: 10.1084/jem.178.1.1. [PubMed: 8391057]. [PubMed Central: PMC2191070].
- Treiner E, Duban L, Bahram S, Radosavljevic M, Wanner V, Tilloy F, et al. Selection of evolutionarily conserved mucosal-associated invariant T cells by MR1. *Nature*. 2003;**422**(6928):164–9. doi: 10.1038/nature01433. [PubMed: 12634786].
- Bolte FJ, Rehermann B. Mucosal-associated invariant T cells in chronic inflammatory liver disease. *Semin Liver Dis.* 2018;**38**(1):60–5. doi: 10.1055/s-0037-1621709. [PubMed: 29471566]. [PubMed Central: PMC6283052].
- Tang XZ, Jo J, Tan AT, Sandalova E, Chia A, Tan KC, et al. IL-7 licenses activation of human liver intrasinusoidal mucosal-associated invariant T cells. *J Immunol*. 2013;**190**(7):3142–52. doi: 10.4049/jimmunol.1203218. [PubMed: 23447689].

- Koay HF, Godfrey DI, Pellicci DG. Development of mucosalassociated invariant T cells. *Immunol Cell Biol.* 2018;96(6):598–606. doi: 10.1111/imcb.12039. [PubMed: 29569752]. [PubMed Central: PMC6446805].
- Koay HF, Gherardin NA, Enders A, Loh L, Mackay LK, Almeida CF, et al. A three-stage intrathymic development pathway for the mucosalassociated invariant T cell lineage. *Nat Immunol.* 2016;**17**(11):1300–11. doi:10.1038/ni.3565. [PubMed: 27668799].
- Jiang X, Lian M, Li Y, Zhang W, Wang Q, Wei Y, et al. The immunobiology of mucosal-associated invariant T cell (MAIT) function in primary biliary cholangitis: Regulation by cholic acid-induced Interleukin-7. *J Autoimmun*. 2018;**90**:64–75. doi: 10.1016/j.jaut.2018.01.007. [PubMed: 29429758].
- Leeansyah E, Ganesh A, Quigley MF, Sonnerborg A, Andersson J, Hunt PW, et al. Activation, exhaustion, and persistent decline of the antimicrobial MRI-restricted MAIT-cell population in chronic HIV-1 infection. *Blood*. 2013;**121**(7):1124–35. doi: 10.1182/blood-2012-07-445429. [PubMed: 23243281]. [PubMed Central: PMC3575756].
- Yong YK, Tan HY, Saeidi A, Rosmawati M, Atiya N, Ansari AW, et al. Decrease of CD69 levels on TCR Valpha7.2(+)CD4(+) innate-like lymphocytes is associated with impaired cytotoxic functions in chronic hepatitis B virus-infected patients. *Innate Immun*. 2017;**23**(5):459–67. doi: 10.1177/1753425917714854. [PubMed: 28606013].
- Rouxel O, Da Silva J, Beaudoin L, Nel I, Tard C, Cagninacci L, et al. Cytotoxic and regulatory roles of mucosal-associated invariant T cells in type 1 diabetes. *Nat Immunol.* 2017;**18**(12):1321–31. doi: 10.1038/ni.3854. [PubMed: 28991267]. [PubMed Central: PMC6025738].
- Keller AN, Corbett AJ, Wubben JM, McCluskey J, Rossjohn J. MAIT cells and MRI-antigen recognition. *Curr Opin Immunol*. 2017;46:66–74. doi: 10.1016/j.coi.2017.04.002. [PubMed: 28494326].
- Kjer-Nielsen L, Patel O, Corbett AJ, Le Nours J, Meehan B, Liu L, et al. MRI presents microbial vitamin B metabolites to MAIT cells. *Nature*. 2012;491(7426):717-23. doi: 10.1038/nature11605. [PubMed: 23051753].
- Ussher JE, Bilton M, Attwod E, Shadwell J, Richardson R, de Lara C, et al. CD161++ CD8+ T cells, including the MAIT cell subset, are specifically activated by IL-12+IL-18 in a TCR-independent manner. *Eur J Immunol.* 2014;44(1):195-203. doi: 10.1002/eji.201343509. [PubMed: 24019201]. [PubMed Central: PMC3947164].
- Howson LJ, Salio M, Cerundolo V. Mr1-restricted mucosal-associated invariant T cells and their activation during infectious diseases. *Front Immunol.* 2015;6:303. doi: 10.3389/fimmu.2015.00303. [PubMed: 26136743]. [PubMed Central: PMC4468870].
- Wallington JC, Williams AP, Staples KJ, Wilkinson TMA. IL-12 and IL-7 synergize to control mucosal-associated invariant T-cell cytotoxic responses to bacterial infection. *J Allergy Clin Immunol.* 2018;**141**(6):2182– 2195 e6. doi: 10.1016/j.jaci.2017.08.009. [PubMed: 28870466].
- Franciszkiewicz K, Salou M, Legoux F, Zhou Q, Cui Y, Bessoles S, et al. MHC class I-related molecule, MRI, and mucosal-associated invariant T cells. *Immunol Rev.* 2016;**272**(1):120–38. doi: 10.1111/imr.12423. [PubMed: 27319347].
- Wong EB, Ndung'u T, Kasprowicz VO. The role of mucosal-associated invariant T cells in infectious diseases. *Immunology*. 2017;**150**(1):45– 54. doi: 10.1111/imm.12673. [PubMed: 27633333]. [PubMed Central: PMC5341498].
- Gold MC, Napier RJ, Lewinsohn DM. MRI-restricted mucosal associated invariant T (MAIT) cells in the immune response to Mycobacterium tuberculosis. *Immunol Rev.* 2015;264(1):154–66. doi: 10.1111/imr.12271. [PubMed: 25703558]. [PubMed Central: PMC4339229].
- Jahreis S, Bottcher S, Hartung S, Rachow T, Rummler S, Dietl AM, et al. Human MAIT cells are rapidly activated by Aspergillus spp. in an APC-dependent manner. *Eur J Immunol.* 2018;**48**(10):1698-706. doi: 10.1002/eji.201747312. [PubMed: 30059139].

- Barathan M, Mohamed R, Vadivelu J, Chang LY, Saeidi A, Yong YK, et al. Peripheral loss of CD8(+) CD161(++) TCRValpha7.2(+) mucosalassociated invariant T cells in chronic hepatitis C virus-infected patients. *Eur J Clin Invest.* 2016;46(2):170–80. doi: 10.1111/eci.12581. [PubMed: 26681320].
- Boeijen LL, Montanari NR, de Groen RA, van Oord GW, van der Heide-Mulder M, de Knegt RJ, et al. Mucosal-associated invariant T cells are more activated in chronic hepatitis B, but not depleted in blood: Reversal by antiviral therapy. J Infect Dis. 2017;216(8):969–76. doi: 10.1093/infdis/jix425. [PubMed: 28968772].
- Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2013.
- Provine NM, Binder B, FitzPatrick MEB, Schuch A, Garner LC, Williamson KD, et al. Unique and common features of innate-like human Vdelta2(+) gammadeltaT cells and mucosal-associated invariant T Cells. Front Immunol. 2018;9:756. doi: 10.3389/fimmu.2018.00756. [PubMed: 29740432]. [PubMed Central: PMC5924964].
- Yong YK, Saeidi A, Tan HY, Rosmawati M, Enstrom PF, Batran RA, et al. Hyper-expression of PD-1 is associated with the levels of exhausted and dysfunctional phenotypes of circulating CD161(++)TCR iValpha7.2(+) mucosal-associated invariant T cells in chronic hepatitis B virus infection. *Front Immunol.* 2018;9:472. doi: 10.3389/fimmu.2018.00472. [PubMed: 29616020]. [PubMed Central: PMC5868455].
- Setsu T, Yamagiwa S, Tominaga K, Kimura N, Honda H, Kamimura H, et al. Persistent reduction of mucosal-associated invariant T cells in primary biliary cholangitis. J Gastroenterol Hepatol. 2018;33(6):1286–94. doi: 10.1111/jgh.14076. [PubMed: 29266628].
- Beudeker BJB, van Oord GW, Arends JE, Schulze Zur Wiesch J, van der Heide MS, de Knegt RJ, et al. Mucosal-associated invariant T-cell frequency and function in blood and liver of HCV mono- and HCV/HIV co-infected patients with advanced fibrosis. *Liver Int*. 2018;**38**(3):458– 68. doi: 10.1111/liv.13544. [PubMed: 28792648]. [PubMed Central: PMC5836956].
- Bolte FJ, O'Keefe AC, Webb LM, Serti E, Rivera E, Liang TJ, et al. Intra-hepatic depletion of mucosal-associated invariant T cells in hepatitis C virus-induced liver inflammation. *Gastroenterology*. 2017;**153**(5):1392–1403 e2. doi: 10.1053/j.gastro.2017.07.043. [PubMed: 28780074]. [PubMed Central: PMC5669813].
- Dias J, Hengst J, Parrot T, Leeansyah E, Lunemann S, Malone DFG, et al. Chronic hepatitis delta virus infection leads to functional impairment and severe loss of MAIT cells. *J Hepatol*. 2019;71(2):301-12. doi:10.1016/j.jhep.2019.04.009. [PubMed: 31100314]. [PubMed Central: PMC6642010].
- Spaan M, Hullegie SJ, Beudeker BJ, Kreefft K, van Oord GW, Groothuismink ZM, et al. Frequencies of circulating MAIT cells are diminished in chronic HCV, HIV and HCV/HIV co-infection and do not recover during therapy. *PLoS One*. 2016;11(7). e0159243. doi: 10.1371/journal.pone.0159243. [PubMed: 27416100]. [PubMed Central: PMC4945024].
- 33. van Wilgenburg B, Scherwitzl I, Hutchinson EC, Leng T, Kurioka A, Kulicke C, et al. MAIT cells are activated during human viral infec-

tions. *Nat Commun*. 2016;7:11653. doi: 10.1038/ncomms11653. [PubMed: 27337592]. [PubMed Central: PMC4931007].

- Zhang QF, Shao JY, Yin WW, Xia Y, Chen L, Wang X, et al. Altered immune profiles of natural killer cells in chronic hepatitis B patients: A systematic review and meta-analysis. *PLoS One*. 2016;**11**(8). e0160171. doi: 10.1371/journal.pone.0160171. [PubMed: 27513564]. [PubMed Central: PMC4981347].
- Cosgrove C, Ussher JE, Rauch A, Gartner K, Kurioka A, Huhn MH, et al. Early and nonreversible decrease of CD161++ /MAIT cells in HIV infection. *Blood*. 2013;**121**(6):951–61. doi: 10.1182/blood-2012-06-436436. [PubMed: 23255555]. [PubMed Central: PMC3567342].
- Dusseaux M, Martin E, Serriari N, Peguillet I, Premel V, Louis D, et al. Human MAIT cells are xenobiotic-resistant, tissue-targeted, CD161hi IL-17-secreting T cells. *Blood*. 2011;**117**(4):1250–9. doi: 10.1182/blood-2010-08-303339. [PubMed: 21084709].
- Ussher JE, Willberg CB, Klenerman P. MAIT cells and viruses. Immunol Cell Biol. 2018;96(6):630–41. doi: 10.1111/imcb.12008. [PubMed: 29350807]. [PubMed Central: PMC6055725].
- Jo J, Tan AT, Ussher JE, Sandalova E, Tang XZ, Tan-Garcia A, et al. Tolllike receptor 8 agonist and bacteria trigger potent activation of innate immune cells in human liver. *PLoS Pathog*. 2014;10(6). e1004210. doi: 10.1371/journal.ppat.1004210. [PubMed: 24967632]. [PubMed Central: PMC4072808].
- Jesteadt E, Zhang I, Yu H, Meierovics A, Chua Yankelevich WJ, Cowley S. Interleukin-18 Is critical for mucosa-associated invariant T cell gamma interferon responses to francisella species in vitro but not in vivo. *Infect Immun.* 2018;86(5). doi: 10.1128/IAI.00117-18. [PubMed: 29507084]. [PubMed Central: PMC5913842].
- Freeman ML, Morris SR, Lederman MM. CD161 expression on mucosaassociated invariant T cells is reduced in HIV-infected subjects undergoing antiretroviral therapy who do not recover CD4(+) T cells. *Pathog Immun.* 2017;2(3):335–51. doi: 10.20411/pai.v2i3.136. [PubMed: 28868514]. [PubMed Central: PMC5578469].
- Won EJ, Ju JK, Cho YN, Jin HM, Park KJ, Kim TJ, et al. Clinical relevance of circulating mucosal-associated invariant T cell levels and their anti-cancer activity in patients with mucosal-associated cancer. *Oncotarget*. 2016;7(46):76274–90. doi: 10.18632/oncotarget.11187. [PubMed: 27517754]. [PubMed Central: PMC5342813].
- Sundstrom P, Ahlmanner F, Akeus P, Sundquist M, Alsen S, Yrlid U, et al. Human mucosa-associated invariant T cells accumulate in colon adenocarcinomas but produce reduced amounts of IFN-gamma. J Immunol. 2015;195(7):3472–81. doi: 10.4049/jimmunol.1500258. [PubMed: 26297765].
- Ling L, Lin Y, Zheng W, Hong S, Tang X, Zhao P, et al. Circulating and tumor-infiltrating mucosal associated invariant T (MAIT) cells in colorectal cancer patients. *Sci Rep.* 2016;6:20358. doi: 10.1038/srep20358. [PubMed: 26837580]. [PubMed Central: PMC4738248].
- Hengst J, Strunz B, Deterding K, Ljunggren HG, Leeansyah E, Manns MP, et al. Nonreversible MAIT cell-dysfunction in chronic hepatitis C virus infection despite successful interferon-free therapy. *Eur J Immunol.* 2016;46(9):2204-10. doi: 10.1002/eji.201646447. [PubMed: 27296288].