

# Human Pegivirus Infection and Lymphoma Risk: A Systematic Review and Meta-analysis

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(See the Editorial Commentary by Kandathil and Balagopal on pages 1229–31.)

**Background.** Human pegivirus (HPgV) is a single-strand RNA virus belonging to the Flaviviridae. Although no definitive association between HPgV infection and disease has been identified, previous studies have suggested an association of HPgV viremia with risk of lymphomas.

**Methods.** We conducted a systematic review and meta-analysis, including 1 cohort study and 14 case-control studies, assessing the association of HPgV viremia with adult lymphomas. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using a random-effects model, overall and by geographic region and lymphoma subtype.

**Results.** The overall OR for lymphoma was 2.85 (95% CI, 1.98–4.11), with statistically significantly elevated ORs observed in 8 of 15 studies. There was a small amount of heterogeneity among studies ( $I^2 = 28.9\%$ ;  $Q = 18.27$ ,  $P = .16$ ), and the funnel plot provided no evidence for publication bias. The strongest association with lymphoma risk was observed for studies from Southern Europe (OR, 5.68 [95% CI, 1.98–16.3]), whereas weaker ORs (with 95% CIs) were observed for studies from North America (2.24 [1.76–2.85]), Northern Europe (2.90 [1.45–18.7]), and the Middle East (2.51 [1.87–7.27]), but all of similar magnitude. Participants with HPgV viremia had statistically significantly increased risks (OR [95% CI]) for developing diffuse large B-cell (3.29 [1.63–6.62]), follicular (3.01 [1.95–4.63]), marginal zone (1.90 [1.13–3.18]), and T-cell (2.11 [1.17–3.89]) lymphomas, while the risk for Hodgkin lymphoma (3.53 [1.48–25.9]) and chronic lymphocytic leukemia (1.45 [1.45–4.66]) were increased but did not achieve statistical significance.

**Conclusions.** This meta-analysis supports a positive association of HPgV viremia with lymphoma risk, overall and for the major lymphoma subtypes.

**Keywords.** human pegivirus; lymphoma; risk; meta-analysis.

Lymphoid neoplasms, including Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), and plasma cell neoplasms, are a heterogeneous group of malignancies. Overall, this group of neoplasms represents the sixth most common cancer in the United States (US), with an estimated 136 690 new cases in 2016, the majority represented by NHL [1]. Several factors have been clearly shown to increase the risk of developing a lymphoid neoplasm, including genetic susceptibility, immunodeficiency, autoimmune disorders, and exposure to physical, chemical, and infectious agents [2]. Among the latter, several large recent studies suggest an association between a common, otherwise nonpathogenic virus called human pegivirus (HPgV)

and NHL [3–5]. HPgV was initially called by 2 names when it was discovered in 1995, GB virus type C (GBV-C) [6] and hepatitis G virus (HGV) [7]. As it was shown not to cause hepatitis or any other known illness, nor was infection identified in the presumed hepatitis patient with the initials “G. B.,” neither name accurately described the virus, and it was reclassified by the International Committee on the Taxonomy of Viruses as a member of the *Pegivirus* genus within the Flaviviridae family [8–10]. A second HPgV found in hepatitis C virus (HCV)-infected humans has more recently been identified, and it is referred to as either HHPgV or HPgV-2 [11, 12].

HPgV is a single-stranded RNA virus transmitted through parenteral, sexual, and perinatal routes [10, 13]. Phylogenetically, HPgV and HPgV-2 are related to HCV, which is also associated with risk of NHL [9, 14–17]. HPgV replicates at high titer, with an average of  $3.28 \times 10^6$  and  $4.76 \times 10^6$  copies/mL in people with and without human immunodeficiency virus (HIV) infection, respectively [18]. Active HPgV infection may persist for decades, although most infections clear within 2 years in immunocompetent hosts [19–21]. The lack of associated hepatic disease

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presumably relates to its tissue tropism, as HPgV does not appear to replicate in the liver. Based on both ex vivo and in vitro studies, HPgV is known to replicate in B and T lymphocytes, including CD4<sup>+</sup> and CD8<sup>+</sup> lymphocytes, spleen, and bone marrow [22–31]. Recently, a rhesus monkey animal model of pegivirus was developed and bone marrow tropism was confirmed [32].

Using a large North American case-control study, we recently reported a positive association of HPgV active infection with risk of lymphoma overall and for all major lymphoma subtypes except HL and CLL [3]. The aim of the present study was to systematically review epidemiologic data on the association between lymphoid neoplasms with HPgV viremia, assess major sources of heterogeneity in the available data, and conduct a meta-analysis.

## METHODS

### Literature Search

Two authors (A. F. and J. T. S.) independently performed a web-based literature search with PubMed/Medline and Google Scholar. The search strategy was based on the following words (all fields): [“hepatitis G virus” (Medical Subject Heading [MeSH]) or “HGV” or “GB virus type C” or “GBV-C” or “human pegivirus” or “HPgV”] and [“lymphoma” (MeSH) or “lymphoproliferative neoplasms” or “Hodgkin lymphoma” (MeSH) or “non-Hodgkin lymphoma” or “chronic lymphatic leukemia”].

### Inclusion Criteria

We included only articles and reports published in English in the period 1997–2018. Eligible publications had to include the prevalence of HGV/GBV-C/HPgV viremia (active infection) in adult lymphoma patients and in a control group. The definition of control groups varied greatly between studies, including patients undergoing a given hospital procedure, blood donors, people living with HCV or HIV, or population-based samples.

### Data Extraction

Data extraction was performed independently by 2 reviewers (A. F. and J. R. C.) and included author, year of publication, country of origin, sample size, method of HPgV RNA detection, and lymphoma classification used. For the case-control studies, we extracted the estimates of odds ratios (ORs) and 95% confidence intervals (CIs) and the variables used for matching and adjustment. For cohort studies, we extracted the source of the cohort, years of follow-up, the outcome measured with 95% CIs, and the variables used for adjustment. Findings for specific lymphoma subtypes were abstracted for studies where the data were reported. Very few discrepancies were identified between the 2 independent reviews, and these were addressed by a joint reevaluation of the original article.

The method of HPgV RNA detection differed among the studies, which leads to some heterogeneity. Specifically, nested reverse-transcription polymerase chain reaction (RT-PCR) increases sensitivity but reduces specificity, while real-time RT-PCR reduces sensitivity [33]. HPgV RNA titers are biphasic in humans

[18], and therefore studies that use real-time RT-PCR will identify only a portion of those with lower titer virus. However, these results will be specific to HPgV (HPgV-1) as the PCR protocols do not detect the more recently described HPgV-2 [11, 12] or HCV [33]. Because HPgV E2 antibodies are detected only after clearance of viremia in >90% of subjects, studies examining E2 antibodies as inclusion criteria, or combined detection of HPgV RNA and E2 antibody, were excluded. Commercial E2 antibody testing methods are no longer available; thus, recent studies do not identify prior infection using a validated methodology [34].

### Quality Assessment

The quality of each study was assessed independently by 2 reviewers (A. F. and J. R. C.) with the Newcastle-Ottawa Scale, consisting of 3 parameters: selection, comparability, and exposure/outcome assessment [35].

### Data Synthesis and Analysis

To provide a quantitative estimate of the association of HPgV active infection with lymphoma risk, the ORs (adjusted, if available) and the corresponding 95% CIs were abstracted from published articles. When the ORs were not given, they were computed from tabular data. We then calculated the summary OR and corresponding 95% CI using a random-effects model of DerSimonian-Laird. The random-effects model accounts for heterogeneity between studies, which is expected in an analysis of this nature. Subset analyses were performed by lymphoma

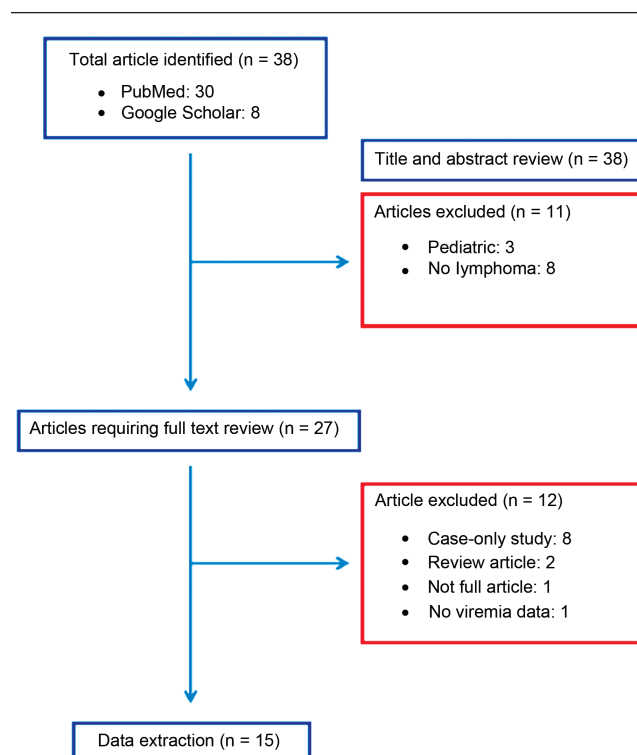


Figure 1. Search results.

**Table 1. Characteristics of the Studies Evaluating the Association Between Human Pegivirus Viremia and Lymphoma Risk**

First Author	Year	Country	Type of Study	Laboratory Method	Classification	Cases					Controls				
						No.	HCV	HIV	HPgV	Time Period	No.	HCV	HIV	HPgV	Source
Zignego	1997	Italy	Case-control	PCR	IWF	150	24.6%	...	6%	...	165	...	1.2%	Healthy subjects	Age, sex
Minton	1998	UK	Case-control	RT-PCR	Not reported	76	...	...	9.2%	Jul 96	100	...	1%	Healthy blood donors	None
Persico	1998	Italy	Case-control	RT-PCR	Not reported	71	4.2%	...	16.9%	...	71	1.4%	1.4%	Healthy subjects	None
Civardi	1998	Italy	Case-control	RT-PCR	Not reported	33	100%	...	3%	...	249	...	2.8%	Not specified	None
Ogino	1999	Japan	Case-control	RT-PCR	IWF	33	12.1%	...	0%	1991–1997	45	4.4%	0%	Hospital patients	Age, sex
Collier	1999	Canada	Case-control	Ligase C	IWF	100	1%	...	5%	Feb–May 1997	100	1%	3%	Cancer patients	Age, sex
De Renzo	2002	Italy	Case-control	PCR	Not reported	227	...	0%	6%	...	110	...	0.9%	Healthy blood donors	Age, sex
Kaya	2002	Turkey	Case-control	PCR	IWF	70	1.4%	...	7.1%	...	70	1.4%	1.4%	Healthy subjects	Age, sex
Giannoulis	2004	Greece	Case-control	RT-PCR	WHO	108	1.9%	...	9.2%	1999–2000	285	...	0.7%	Blood donors	None
Ernst	2011	Germany	Case-control	...	Not reported	33	...	100%	30.3%	...	584	...	23.6%	HIV patients	None
Krajden	2010	Canada	Case-control	RT-PCR	WHO	553	2.2%	...	4.5%	...	438	0.9%	1.8%	Healthy subjects	Age, sex, region
Khodavandi	2011	Iran	Case-control	RT-PCR	Not reported	70	...	...	2.8%	...	100	...	1%	Other patients	None
Rezaeian	2012	Iran	Case-control	PCR	WHO	140	2.9%	...	4.3%	2007–2011	120	0%	2.5%	Hospital patients	None
Chang	2014	US	Cohort	RT-PCR	WHO	658	...	...	1.8%	1993–2001	1316	...	0.5%	Healthy subjects	Age, sex, race/ethnicity
Fama	2018	US	Case-control	RT-PCR	WHO	2094	...	...	10.1%	2002–2015	1572	...	5%	Hospital patients	Age, sex, region

Abbreviations: HCV, hepatitis C virus; HIV, human immunodeficiency virus; HPgV, human pegivirus; IWF, International Working Formulation; PCR, polymerase chain reaction; RT-PCR, reverse-transcription polymerase chain reaction; UK, United Kingdom; US, United States; WHO, World Health Organization.

subtype and geographic area. Publication bias was also assessed by direct examination of a funnel plot. Heterogeneity among studies was assessed using the  $I^2$  statistic and Cochran  $Q$  statistic. According to Higgins,  $I^2$  values of 25%, 50%, and 75% are arbitrarily considered to have low, moderate, and high heterogeneity, respectively [36]. All statistics and graphs were obtained using the R packages meta [37] and rmeta [38] in R version 3.4.2.

## RESULTS

### Search Results

The results of our search strategy are summarized in Figure 1. A total of 38 articles were identified. We excluded 11 studies after review of the title and abstract: 8 had no reference to lymphoma and 3 were conducted in pediatric patients. After a detailed full text review of the 27 remaining articles, we excluded 12 articles: 8 were case-only studies, 2 were reviews, 1 was not available in full form (abstract only), and 1 did not report any viremia data. A total of 15 articles (14 case-control studies [3, 5, 39–50] and 1 cohort study [4]) met the inclusion criteria.

### Characteristics of the Studies Included

The main characteristics of the published studies that evaluated the association of active HPgV infection with lymphoma risk are shown in Table 1. Geographically, 5 studies originated from Southern Europe, 2 from Northern Europe, 4 from North America, 3 from the Middle East, and 1 from Japan. Nine of

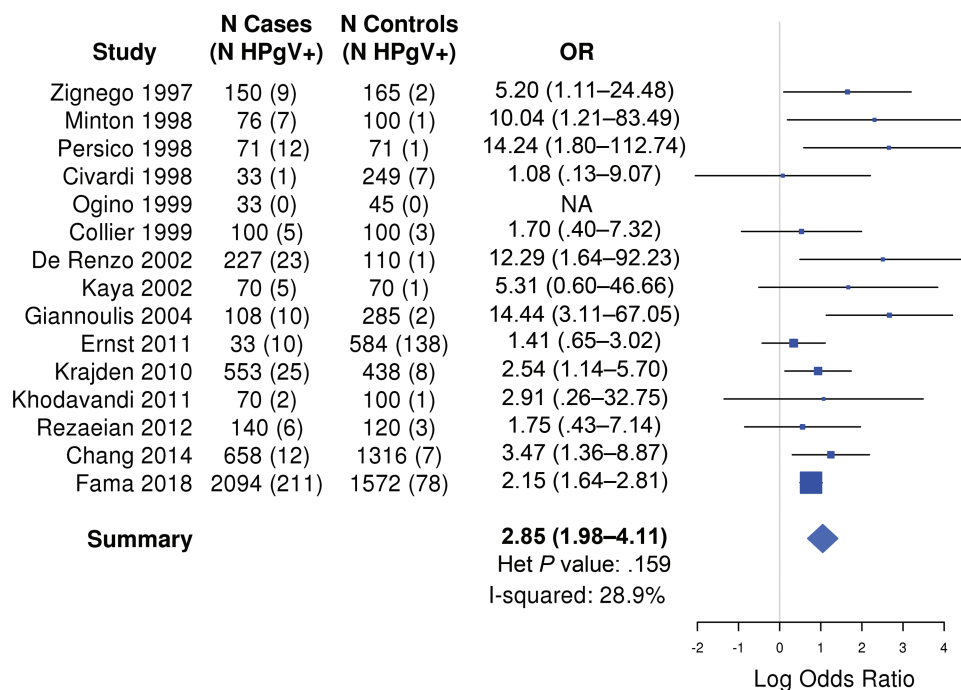
the studies included HCV- or HIV-coinfected subjects and controls. The prevalence of HPgV viremia varied widely across studies, ranging from 0% reported in the small Japanese study [43] (33 cases and 45 controls) to 30% reported in the study conducted in 33 people with HIV infection [48]. Fourteen of 15 studies showed an increased lymphoma risk with HPgV active infection (all OR > 1.40), 8 of which were statistically significant. Four studies included analyses by NHL subtype.

### Quality Assessment Results

The quality assessment of the studies included in this meta-analysis is shown in Supplementary Table 1; only 3 studies [3–5] were rated as good based on the Newcastle-Ottawa Scale.

### Main Effect

The summary OR from the 15 studies, based on 4416 cases (338 [7.6%] HPgV viremia positive) and 5502 controls (258 [4.6%] HPgV viremia positive), was 2.85 (95% CI, 1.98–4.11;  $I^2 = 28.9\%$ ), with statistically significantly elevated ORs observed in half of the studies (Figure 2). The funnel plot showed a good symmetrical distribution of the studies, consistent with the absence of publication bias (Supplementary Figure 1). If this was a causal association, then using an OR or 2.85 as an estimate of the relative risk and prevalence ranges based on the study from British Columbia (1.8%) [5] and the study from the United States (US) (5.0%) [3], the population attributable risk would be 3.2% or 8.5%, respectively.



**Figure 2.** Odds ratios and corresponding 95% confidence intervals for risk of lymphoma by human pegOvirus viremia positivity in case-control and cohort studies. Abbreviations: Het, heterogeneity; HPgV, human pegivirus; NA, not applicable; OR, odds ratio.

## Subset Analyses

### Coinfections

After excluding known HIV-positive cases and controls (leaving 8 studies with available data), the meta-analysis of HPgV and lymphoma revealed an OR of 2.83 (95% CI, 1.64–4.74;  $I^2 = 32.6\%$ ; [Supplementary Figure 2A](#)), largely unchanged from the overall meta-analysis. After excluding known HCV-positive cases and controls (leaving 10 studies with available data), the meta-analysis of HPgV and lymphoma revealed an OR of 4.43 (95% CI, 2.75–7.15;  $I^2 = 3.6\%$ ; [Supplementary Figure 2B](#)), much stronger than the overall meta-analysis. Only 1 study had data on hepatitis B virus (HBV) infection [49], and after excluding HBV<sup>+</sup> cases and controls it found a weak positive association of HPgV and lymphoma (OR, 1.46 [95% CI, .09–23.7]), but was based on small numbers (1 exposed case and 1 exposed control).

### Good-Quality Studies

When the analysis was restricted to the 3 studies rated as “good” on the Newcastle-Ottawa Scale ([Supplementary Figure 3](#)), there was an approximately 20% attenuation of the association to an OR of 2.25, with 95% CIs (1.76–2.88) that were similar to the overall meta-analysis.

### Geographic Area

The strongest association was observed for studies from Southern Europe (OR, 5.68 [95% CI, 1.98–16.33]), while similar ORs were observed for studies from North America (OR, 2.24 [95% CI, 1.76–2.85]), Northern Europe (OR, 2.90 [95% CI, .45–18.65]), and the Middle East (OR, 2.51 [95% CI, .87–7.27]), although the latter 2 estimates were not statistically significant ([Figure 3](#)).

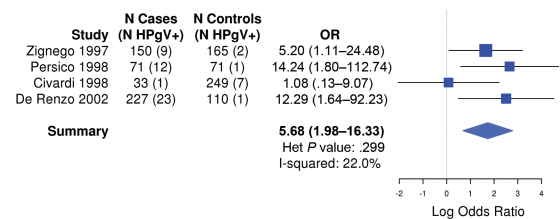
### Lymphoma Subtypes

Elevated risk was observed for follicular lymphoma based on 3 studies (OR, 3.01 [95% CI, 1.95–4.63]), diffuse large B-cell lymphoma based on 3 studies (OR, 3.29 [95% CI, 1.63–6.62]), marginal zone lymphoma based on 2 studies (OR, 1.90 [95% CI, 1.13–3.18]), T-cell lymphoma based on 2 studies (OR, 2.11 [95% CI, 1.14–3.89]), CLL based on 2 studies (OR, 1.45 [95% CI, .45–4.66]), and HL based on 2 studies (OR, 3.53 [95% CI, .48–25.88]), with the latter 2 estimates not achieving statistical significance at  $P < .05$  ([Figure 4](#)). None of the studies identified a characteristic clinical presentation or prognostic significance to lymphomas found in HPgV-infected patients.

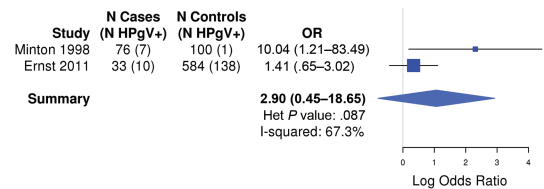
## DISCUSSION

In this first meta-analysis of HPgV viremia with lymphoma risk, we found a strong and statistically significant association with lymphoma risk overall (OR, 2.85) and for all of the major subtypes, except for CLL/SLL and HL. The association was much stronger in Southern Europe, and while risk estimates were weaker for North America, Northern Europe, and

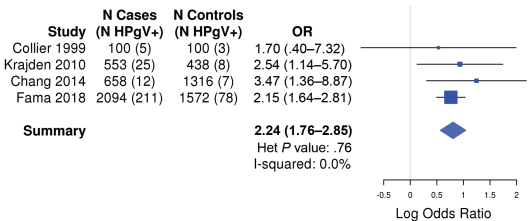
### a) Southern Europe



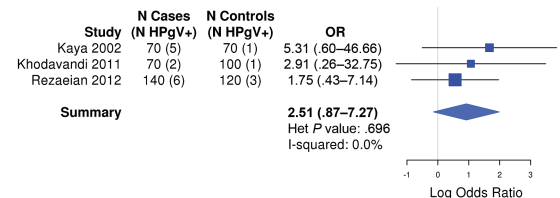
### b) Northern Europe



### c) North America



### d) Middle East



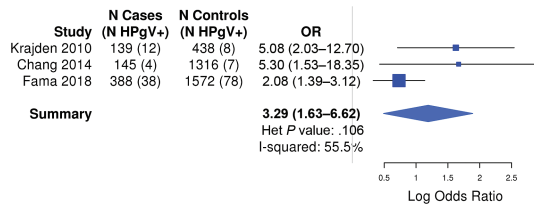
**Figure 3.** Odds ratios and corresponding 95% confidence intervals for risk of lymphoma by human pegivirus viremia positivity, by geographic region. Abbreviations: Het, heterogeneity; HPgV, human pegivirus; OR, odds ratio.

the Middle East, they were all of similar magnitude. While the results were robust, only 3 of 15 studies were rated as being of good methodologic quality, and the association attenuated approximately 20% to an OR of 2.25, suggesting the poorer quality studies slightly overestimated the association of HPgV viremia and lymphoma risk. We also did not find evidence for a strong role of coinfection by either HIV or HCV in explaining the HPgV and lymphoma association, noting we were not able to simultaneously assess HIV and HCV nor assess coinfection by HBV based on the published data. All but 1 study [4] was a case-control study and collected specimens at diagnosis, raising concerns about reverse causality. However, the results from case-control studies were consistent with the findings from a prospective cohort study [4] that used specimens banked before lymphoma diagnosis.

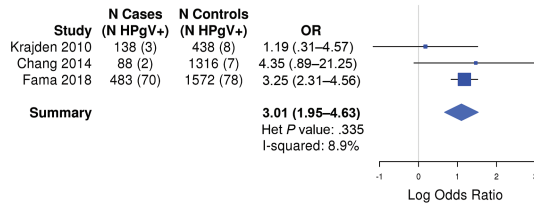
These results could have public health significance related to the safety of the blood supply. Approximately 2% of healthy US



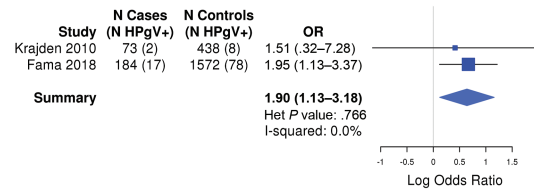
a) DLBCL



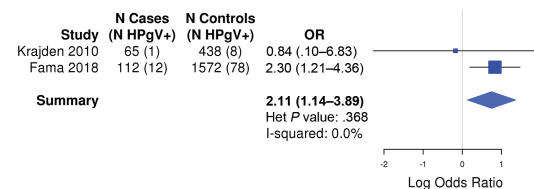
b) Follicular lymphoma



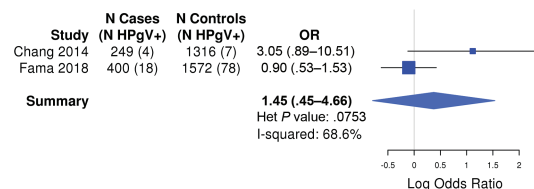
c) Marginal zone lymphoma



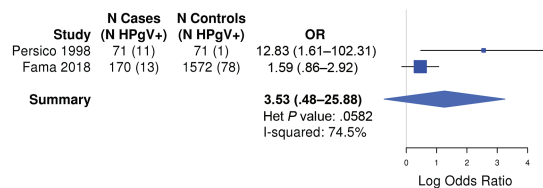
d) T-cell lymphoma



e) CLL



f) Hodgkin lymphoma



**Figure 4.** Odds ratios and corresponding 95% confidence intervals for risk of lymphoma by human pegivirus viremia positivity, by lymphoma subtype. Abbreviations: CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; Het, heterogeneity; HPgV, human pegivirus; OR, odds ratio.

blood donors are viremic with HPgV at the time of blood donation, while individuals with sexually transmitted infections, people living with HIV, and intravenous drug users have a much higher rate of exposure and viremia, with a cross-sectional

viremia prevalence of approximately 20%, as reviewed by Mohr and Stapleton [51]. To date, no definitive association between HPgV and clinical disease has been identified, and thus the US Food and Drug Administration has not recommended nor required screening of blood donors for HPgV viremia [52, 53]. This means that up to 200 000 units of GBV-C-contaminated blood products are transfused into recipients each year in the US [54]. If HPgV infection is truly a risk for lymphoma, the virus might represent a biomarker that potentially can be treated or prevented, raising a legitimate concern about the need to screen for and exclude HPgV-viremic donors from blood donation.

The overall association estimated by the random-effects model should be interpreted as the average of the ORs across the studies, and the main sources of heterogeneity of OR estimates between available studies must be considered before drawing conclusions on the real strength of the association between HPgV active infection and lymphoma. The most relevant source of heterogeneity was the prevalence of HPgV across the study subjects. Its wide variation might depend on the source of controls between the studies, including healthy blood donors, patients undergoing a given hospital procedure, people with HCV or HIV infection, or population-based samples. Another possible source of heterogeneity is the sensitivity of different methods for HPgV RNA detection, as noted above. We also only included results for viremic participants, and not those who were seropositive alone given concerns about the reproducibility of nonvalidated antibody test methods [34]. Furthermore, the relationship between prior viral clearance and NHL has not been clearly demonstrated and the prospective cohort study suggested that the association was more highly associated with active viremia [4]. If prior viremia is associated with NHL, our meta-analysis may underrepresent the contribution of HPgV to lymphoma. We were not able to fully assess the potential role of coinfections, particularly by HBV or simultaneous HCV and HBV. While most studies did not have data on transfusion history, a positive association was observed in studies that either excluded prior transfusion [45, 46] or adjusted for it the analysis [3, 5, 44]. An additional limit of our meta-analysis is the lack of adjustment for other potential confounding factors in most of the studies included in the analysis; however, the methodologically strongest studies in the analysis [3–5] observed positive associations after adjusting for a variety of potential confounders.

The biological mechanisms that may contribute to a role for HPgV viremia in lymphomagenesis include its being a lymphotropic virus that may cause persistent infection in both T and B lymphocytes [24, 30, 31]. In cell lines derived from HIV-infected patients, HPgV reduces Fas-mediated apoptosis [55] and virus impairs T-cell receptor and interleukin 2 receptor signaling in primary and transformed T-cell lines [56, 57] and in patients with HCV infection [58], all of which may contribute to subclinical impairment of immune surveillance. HPgV also influences cytokine and chemokine gene expression in lymphocytes

in vitro and in cells obtained from infected individuals, potentially influencing immune response [59–62]. Finally, persistent lymphocyte infection could lead to DNA mutation and potentially malignant transformation. Alternatively, it could simply be an epiphenomenon attributable to both uncleared HPgV and lymphoma being more likely to be found in patients with sub-optimal immune function.

In conclusion, this meta-analysis confirms that HPgV active infection is associated with an increased risk of developing lymphoma, including the major NHL subtypes except HL and CLL. Further epidemiological studies using banked samples from prospective cohort studies are needed to rule out reverse causality and understand latency, along with a comprehensive assessment of the potential role of coinfections (particularly for HBV) and blood transfusion. In addition, studies are needed to clarify biologic mechanisms underlying this association.

### Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyrighted and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

### Notes

**Author contributions.** A. F., J. T. S., and J. R. C. designed the study, identified the relevant publications, and abstracted key data elements. M. L., M. J. M., and S. L. S. conducted the statistical analysis. All authors interpreted the results, reviewed an initial draft of the manuscript, and approved the final version.

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