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Complete remission of Hodgkin Lymphoma after a concurrent infection with COVID-19: systematic review and meta-analysis

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Abstract

Through December 2019, novel coronavirus (SARS-CoV-2) pneumonia (COVID-19) was reported in Wuhan and has since rapidly spread throughout China. Hodgkin lymphoma represents a heterogeneous hematological malignancy, which is characterized by immunosuppression. There are no clearly defined risk factors for the development of this disease and the cause of remains unknown. Factors shown to be associated with Hodgkin include familial factors, viral exposures, and immune suppression. An electronic search was performed to identify all studies reporting on the management of Hodgkin lymphoma patients during the COVID-19 pandemic. The PubMed/MEDLINE database was searched on October 30th, 2019, to January 30th. 2022. The search strategy was SARS-CoV-2 or COVID-19 and Hodgkin lymphoma. We aimed to clarify the clinical outcome of COVID-19 in patients with Hodgkin lymphoma through systematic review and meta-analysis.

Keywords: SARS-CoV-2, Hodgkin lymphoma, Complete remission

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Introduction

The coronavirus disease 2019 (COVID-19) global pandemic has put an unprecedented strain on cancer care [1]. Most directly, the initial months were marred by fears of immunocompromised patients becoming opportunistic hosts to this deadly virus. Non-emergent treatments were postponed, and it has been well reported that preventative cancer screening significantly regressed in the United States in 2020 [3]. A year-to-year survey of Medicare claims demonstrated a staggering 70% decrease in new patient evaluation and management visits at the height of the pandemic in April 2020 [4].

There is growing evidence that patients with hematological malignancies have poor outcomes following COVID-19 infection [5].

In a cohort study of over 17 million adult NHS patients, an increased risk of mortality was reported in COVID-19 positive patients diagnosed with a hematological malignancy within the last 5 years, greater than that seen in patients with non-hematological malignancies or with other causes of immunosuppression [6].

A number of single center cohort studies of COVID-19 outcomes in patients with hematological cancers report mortality of 32–62% [7], which is higher than the predicted population mortality. As we potentially enter a 'second wave' of COVID-19 infections, continuing to collate national and international outcomes data on this high-risk group will be key to identifying patient-specific risk factors and optimizing treatment and prognosis [8].

Hodgkin lymphoma (HL) affects approximately 8480 new patients In the United States each year. The disease has a bimodal distribution with an increased incidence in young adults as well as in patients 55 years and older.

There are no clearly defined risk factors for the development of this disease and the cause of HL remains unknown. Factors shown to be associated with HL include familial factors, viral exposures, and immune suppression [9]. Same sex siblings of patients with HL have a 10-fold higher risk for developing the disease.

While these familial factors may suggest a genetic cause for this disease, research also suggests that an abnormal immune response to infection may play a role in the pathogenesis of HL. Epidemiologic and serologic studies have implicated Epstein-Barr virus (EBV) in the etiology of HL and the EBV genome was detected in tumor specimens from patients with HL [10].

Other childhood infectious illnesses including chickenpox, measles, mumps, rubella, and pertussis, however, are negatively associated with the risk of HL and are possibly protective [11]. There is also an association with human immunodeficiency (HIV) infection, in that HIV infected patients have a significantly increased risk of HL when compared to the general population [12]. Overall, HL in immunosuppressed patients, including those who are HIV positive, is associated with advanced stage of disease at presentation, unusual sites of disease, and a poorer outcome after initial therapy [13].

The objective of this systematic review and meta-analysis to clarify the clinical outcome of COVID-19 in patients with Hodgkin lymphoma through.

Methods

A review of the literature reporting on SARS-CoV-2 infection in lymphoma patients was conducted. We focused on the relationship with Hodgkin lymphoma characteristics and the clinical course of COVID-19 infection. An electronic search was performed to identify all studies reporting on the management of Hodgkin lymphoma patients during the COVID-19

pandemic. The PubMed/MEDLINE database was searched on October 30th, 2019, to January 30th. 2022. The search strategy was SARS-CoV-2 or COVID-19 and Hodgkin lymphoma.

Results

COVID related signs and symptoms, COVID management

The most common clinical findings at presentation among hospitalized patients with Hodgkin lymphoma concurrent infection with COVID-19 were pneumonia (86%) and fever (79%), followed by dyspnea (60%). Fever represented the relatively most common sign or symptom in not-admitted patients. Of hospitalized patients, 60% were admitted in various departments of internal medicine care, 29% at the infectious disease departments, and 16% in ICU Figure 1 and Table 1.

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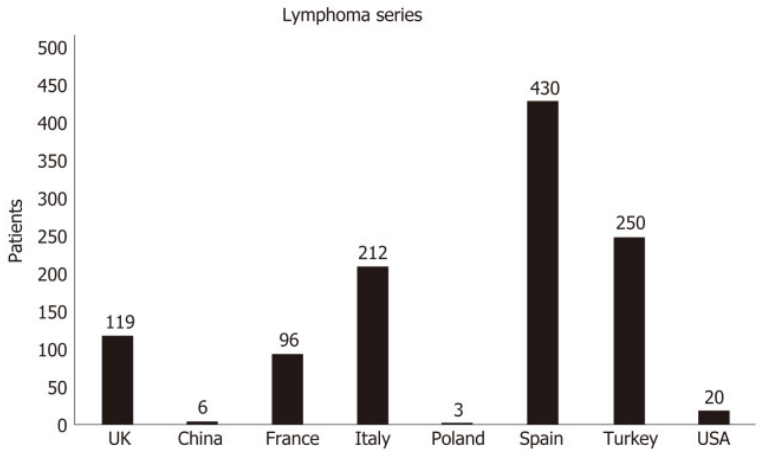

Figure 1.

Number of Hodgkin lymphoma patients described all over the world in largest hematologic malignancy studies. UK: United Kingdom; USA: United States of America.

Table 1.

Case reports and case series of coronavirus disease 2019 infection in Hodgkin lymphoma patients

Sex	Age	Details on HL treatment	Outcome of COVID-19 infection	Global outcome
F	24 yr	ABVD	Recovered	Dead
F	55 yr	ABVD+radiation	Not recovered	Dead
F	36 yr	ABVD+radiation	Not recovered	Alive
		Pembrolizumab	Recovered	Alive
M	50 yr	ABVD	Recovered	Alive
F	43 yr	Obinotuzumab maintenance	Recovered	Alive
M	31 yr	Ibrutinib	Recovered	Alive
M	NR	ABVD	Recovered	Alive
F	38 yr	ABVD+radiation	Recovered	Alive
M	20 yr	R-ICE	Not recovered	Alive
M	35 yr	ABVD+radiation	Not recovered	Dead
M	55 yr	Brentuximab	Not recovered	Dead
M	33 yr	A + AVD	Recovered	Alive
M	38 yr	ABVD	Not recovered	Dead
M	37 yr	ABVD	Recovered	Alive
F	31 yr	ABVD	Recovered	Dead
M	33 yr	ABVD+radiation	Recovered	Dead
F	46 yr	ABVD+radiation	Not recovered	

Figure 2, showed that liver function tests demonstrated an aspartate aminotransferase (AST) level of 91 U/L, alanine aminotransferase (ALT) level of 65 U/L, and alkaline phosphatase level of 166 U/L. There was initial concern for tick-borne illnesses given her constellation of symptoms, frequent outdoor activity, cytopenia with transaminitis, and residence in New England.

A surveillance COVID-19 polymerase chain reaction (PCR) test, performed in the emergency room per hospital protocol, returned positive.

The presenting symptoms and laboratory abnormalities were attributed to COVID-19 infection. With strict isolation precautions, the patient's daily focused physical examination masked several critical findings, including palpable right supraclavicular, axillary, and inguinal adenopathy. Serial laboratory studies over the initial 48 hours of admission demonstrated worsening cytopenias and progressive hepatic injury despite a stable respiratory status.

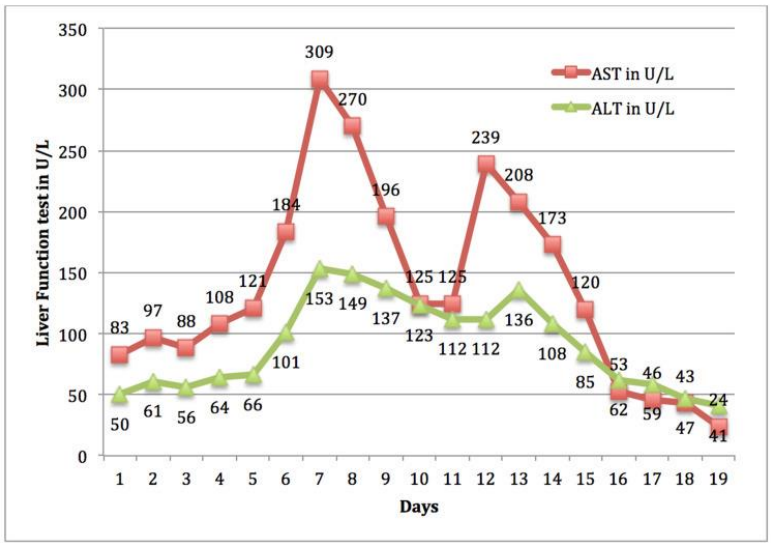

Figure 2.

The liver function test trend is shown in the trend of AST and ALT in Hodgkin lymphoma. [Adapted from Cureus. 2022 Feb; 14(2): e22635].

Overall survival of COVID-19 with Hodgkin lymphoma

Overall, 199 patients died after a median follow-up of 50 days. Overall, the 30- and 90-days mortality was 11% (95% CI, 11% to 15%) and 20% (95% CI, 26% to 22%), respectively, as shown in Figure 3. The vast majority of deaths were due to COVID-19 infection or complications related to the infection (93%, vs 11 unrelated, 4%). Unrelated deaths were due to Hodgkin lymphoma progression in 12 of the 13 cases. As expected, patients admitted to the hospital had significantly worse OS than patients not admitted ($P < .005$), as shown in Figure 4. The CFR of admitted vs not-admitted patients was 32.5% and 3.3%, respectively.

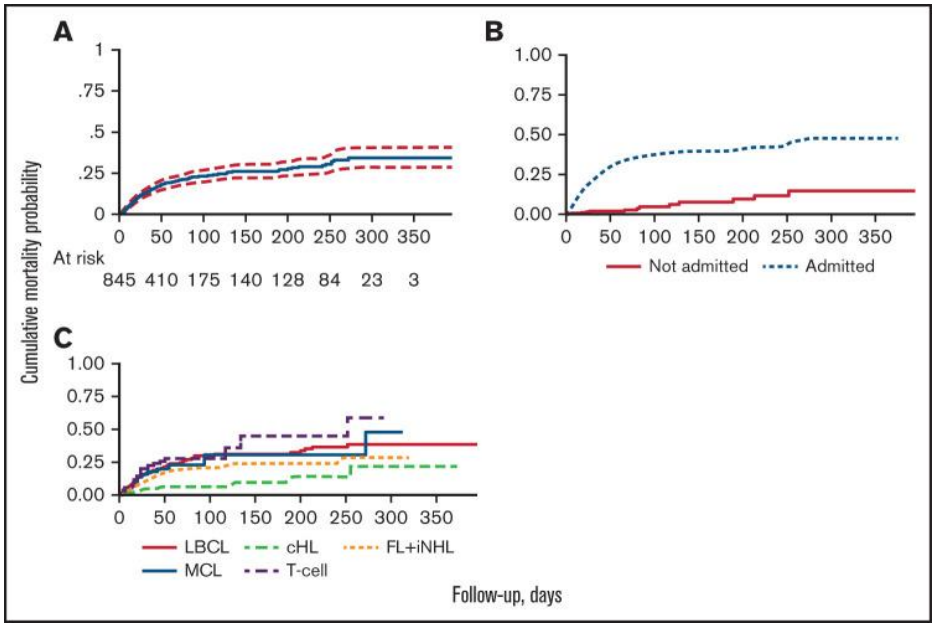

Figure 3.

Overall survival for enrolled patients. Kaplan-Meyer curves for overall survival in all enrolled patients [Adapted from.

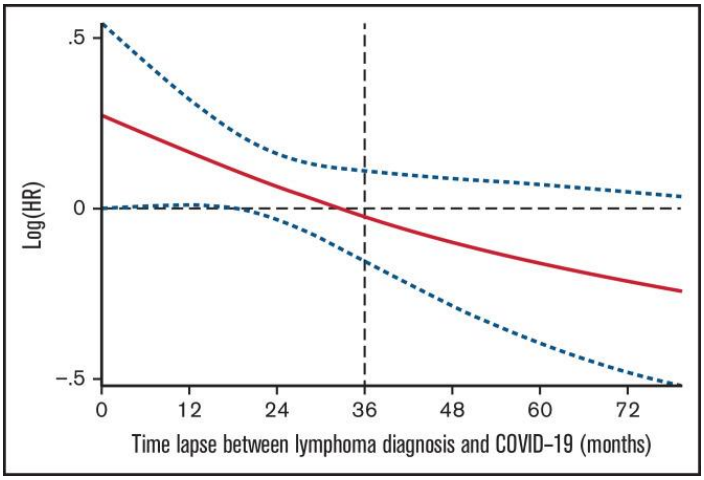

Figure 4.

Risk of death related with the time from lymphoma diagnosis to COVID infection.

Discussion

Over the last four decades, advances in radiation therapy and the addition of combination chemotherapy have significantly increased the cure rate of patients with HL [14]. Currently, more than 80% of all newly diagnosed patients younger than 60 years are likely to be cured of their disease [15].

Recent studies indicated a clear decrease in peripheral lymphocytes and natural killer cells (NK) in Covid-19 patients [16]. The lymphodepletion induced by Sars-Cov-2 has a pivotal diagnostic role and represents a valid prognostic tool. Total lymphocytes, CD4+ T cells, CD8+ T cells, B cells and Natural Killer (NK) cells decreased in Covid-19 patients and severe cases had a lower level than mild cases [17]. In recovered Covid-19 patients is documented an increase in lymphocytes count and related subsets. No further significant changes are detected in unresponsive patients [18].

In Covid-19 infected patients a clinical constellation of cytokine storm, respiratory failure and eventually death is reminiscent of a “hyperferritinemic syndrome”. The inflammatory microenvironment may shift the balance to reduce NK cell effector functions in both Covid-19 and inflammatory forms of secondary hyperferritinemic syndrome [19]. Elevated IL-6 and IL-10 levels, as observed in Sars-CoV2-infected patients have the capacity to directly reduce NK cell cytotoxicity and increase the expression of NKG2A, which is important in killing virally infected cells [20].

It has been shown that Sars-CoV2 binding to ACE2 may infect NK cells to suppress their functions, as NK cells express angiotensin converting enzyme 2 (ACE2). Although not published in Covid-19, other RNA viruses that cause acute pulmonary infections promote NK cells apoptosis and reduce their cytotoxicity following their infection [21].

Sars-CoV2 and the subsequent immune cell inflammatory responses suppress NK cells cytotoxicity which promotes a severe cytokine release syndrome, and inadequate immune responses [22].

Our previous report predicted that the SARS-CoV-2 infection pathway is involved in crosstalk with other viral pathways, including EBV [23]. Co-infection of EBV in COVID-19 patients is not uncommon, and in COVID-19 patients, reactivation of EBV has been reported, which may be associated with disease severity and other symptoms of long COVID-19 [24]. Additionally, patients with lymphoproliferative disorders showing immunodeficiency and post-traNSPlantation patients subjected to immunosuppression, the synergistic action of EBV and SARS-CoV-2 may increase the fatality rate [25].

The cHL patient of Challenor and Tucker was EBV positive [26], and the LMP-1 of EBV is the main oncogenic protein of EBV that activates oncogenic signaling through activation of NF-κB, JAK/STAT, and PI3K/AKT pathways through its cytoplasmic TRAFs and TRADD

binding motifs [27]. Contrary to the reported potential synergistic association between EBV and SARS-CoV-2 [28], in our analysis (as per our third hypothesis), other found that the 3CLpro/Mpro, NSP7, NSP10, and S proteins of SARS-CoV-2 may interact at the TRADD binding sites of LMP-1 thus blocking the access of TRADDs to LMP-1, and this interaction may inhibit the LMP-1-mediated NF-kB oncogenic signaling to induce remission [29]. However, further investigations are required to validate these interactions and their outcomes in lymphoma remission [30].

NK/T-cell lymphoma and NK-cell leukemias are aggressive malignancies. NK/T-cell lymphomas are almost exclusively extranodal. Lymphomas occur commonly in the nasal and upper aerodigestive region. Rare cases are disseminated with lymphoadenopathy, hepatosplenomegaly, and a leukemic phase [31-33]. Neoplastic cells are surface CD3-, cytoplasmatic CD3+, CD56+ cytotoxic molecule positive and Epstein Barr virus (EBV) positive with germline T-cell receptor gene. EBV infection is latent and not lytic in the lymphoma cells, and EBV-DNA is an accurate biomarker of tumor load [34]. Serial EBV-DNA monitoring is useful for assessing response and detecting recurrence during chemiotherapy [35-39].

Conclusion

This article showed that Covid-19 infection might have role in transient remission of Hodgkin lymphoma as shown by reduction of NK neoplastic cells and plasmatic EBV-DNA drop. Tumor associated infection (EBV-related) and possibly preexisting autoimmunity (AHIA) could compound propensity for spontaneous remission.

Ethical Approval

The study was approved by the Ethical Committee.

Conflicts of Interest

The authors declare that they have no competing interests.

Authors' Contributions

All authors shared in conception, design of the study, acquisition of data, and manuscript writing, the critical revising and final approval of the version to be published.

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