

Viral Respiratory Infections in Patients with Cancer

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Abstract

Context: Cancers are among the gravest causes of the intensive immunodeficiency and provide favorable conditions for severe respiratory tract infections.

Evidence Acquisition: Using various keywords related to the subject matter, articles were analyzed in PubMed and appropriately selected for review.

Results: In patients with cancer, some viral respiratory infections such as HRSV, Influenza virus, HCMV, HMPV and HPIV are prevalent.

Conclusions: Viral respiratory infections in cancer patients are common and can worsen the patients' condition and disrupt the treatment process. Therefore, prevention and treatment of respiratory viral infections in cancer patients is important.

Keywords: Virus, Respiratory Infection, Cancer

1. Context

The accumulated evidence has supported involvement of viral respiratory infections in upper and lower respiratory tract illness around the world (1). In healthy persons, by the age of 2 - 60 years, these infections are usually suppressed by the host's immune system, symptoms are limited to upper respiratory tract and infected individuals only experience slight and transient common cold-like symptoms (2). However, in children younger than 2 years, adults older than 65 years, patients with chronic lung disease, neuromuscular disease, airway anomalies, asthma or hemodynamically significant congenital heart disease and also in immunocompromised patients, the respiratory symptoms are more prevalent, severe and life-threatening (3-5). There are different agents causing immunodeficiency in human body. Among these, some types of cancers, especially hematological malignancies (e.g. chronic lymphoid leukemia and chronic myeloid leukemia) are among the important causes of the intensive immunodeficiency and provide favorable conditions for severe acute respiratory tract illnesses by directly affecting the immune system (6-10). This article reviews the importance of viral respiratory agents in some types of cancers.

2. Evidence Acquisition

In this review, decided decision has been made to take a glance at the prevalence of viral respiratory infections in cancer patients. Using keywords such as cancer, virus and respiratory infection, a PubMed search was conducted to

find high quality articles pertaining to the central theme of this paper.

3. Results

3.1. Human Respiratory Syncytial Virus (HRSV)

Human respiratory syncytial virus (HRSV) is internationally classified as a member of pneumovirus genus from the subfamily of pneumovirinae and this subfamily is a subset of the virus family called paramyxoviridae. This virus is divided into two major antigenic groups A and B on the basis of the G protein variability. The genome of the virus is a linear single stranded negative-sense RNA molecule containing 10 genes which encodes 11 proteins (2, 11, 12). M protein acts as a bridge between the envelope and ribonucleoprotein (RNP) of the virus and keeps these two parts tightly together, and cooperates in assembly and budding of the virion (12, 13). M protein also binds simultaneously to cellular actin (the main component of cell cytoskeletal microfilaments) and the viral RNPs, facilitating transport of these viral structures to the cellular plasma membrane location (14).

HRSV can cause upper and lower respiratory tract illness in all ages but the site of infection and severity of symptoms changes by the age and health status (4). HRSV is defined as the agent of childhood acute bronchiolitis and pneumonia around the world, with a frequency of 12% - 52%. Especially, in hospitalized children younger than 2 years, this frequency is estimated about 50% - 90% in acute

bronchiolitis and 5% - 40% in pneumonia (15). 90% of children are infected with RSV during the first 2 years of life and up to 40% of them will develop acute lower respiratory tract infection (LRTI). In the United States, from 1980 to 1996, bronchiolitis, caused by RSV, was a common agent of hospitalization of infants less than one year of age, with the rate of more than 100,000 per year (16). In a study in 2005, the worldwide incidence of HRSV-associated ARTI in children younger than 5 years was evaluated about 33.8 million new episodes with at least 3.4 million episodes of LRTI necessitating hospital admission. About 66,000 to 199,000 children younger than 5 years died of HRSV associated acute lower respiratory tract infection in 2005, of which 99% occurred in developing countries (17). In Iran, HRSV is responsible for 20% acute respiratory infection in younger children (18-20). Infection by this virus is considered as one of the most important causes of seasonal respiratory complications in adults (2). 25% of mortality attributed to respiratory infections in cold seasons is due to HRSV, which in this respect is like influenza virus. Approximately 80% of mortalities caused by respiratory infection of HRSV occur in the elderly. General symptoms include fever, headache, myalgia, sneezing, sore throat, dry cough, rhinorrhea, bronchitis and otalgia, but the infection can spread to the lower respiratory tract of the risk groups mentioned above, which subsequently leads to wheezing, tracheobronchitis, severe bronchiolitis and pneumonia (2).

HRSV infection can cause considerable morbidity and mortality in leukemia patients. However, treatment with aerosolized ribavirin may prevent spreading of infection to the lower respiratory tracts and developing pneumonia in patients at the stage of upper respiratory tract infection (URTI).

Torres et al worked on outcomes of HRSV infection in leukemia patients. 52 patients with the median age of 47 years (range from 1-83 years) were evaluated, from which 34 patients (65%) were male and 18 patients (35%) had acute leukemia. 46 patients were admitted to the hospital of which 27 (52%) developed pneumonia secondary to HRSV. 5 (19%) out of the 27 cases died because of pneumonia. There was a trend toward a higher rate of progression from URTI to pneumonia in males compared to females (74% vs 56%). Viral and bacterial co-infections were diagnosed in nine (17%) of all patients five of which involved the lung (21). In a study performed between 2004 and 2009 on the molecular epidemiology of HRSV subgroups A and B in Irish adults with hematological malignancy, a total of 980 samples were evaluated for infection by this virus via immunofluorescence, from which 60 evaluable samples were HRSV-positive. The patients had various blood malignancies covering chronic myeloid

leukemia (10 cases), chronic lymphocytic leukemia (10 cases), acute lymphoblastic leukemia (10 cases), acute myeloid leukemia (9 cases), non-Hodgkin's lymphoma (8 cases), multiple myeloma (7 cases), mantle cell lymphoma (2 cases), and aplastic anemia (2 cases). Nearly 50% (n = 31) of these patients were hospitalized for treatment with aerosolized ribavirin because of severe complications of HRSV infection. The A subgroup frequency was 52% versus 48% for subgroup B. Among the eight genotypes of HRSV A, two of them GA2 and GA5 were observed in this study. The only identified genotype from subgroup B was the BA genotype (22).

In 1997, Mazzulli et al. performed a molecular characterization study on a nosocomial outbreak of HRSV in an adult leukemia-lymphoma ward in the PMH cancer hospital. BAL samples were collected from 45 patients and then cultured on rhesus monkey kidney (RMK), MRC-5 and HEp-2 cell lines. Six cultures were positive for HRSV of which 5 cultures also had positive results by direct immunofluorescence staining. Then RT-PCR was performed on BAL specimens and RNAs extracted from the HRSV positive cultures. Test results were positive for 5 of the 6 cultures and also for two additional BAL specimens. After sequencing six GB3 and one GA5, genotypes were discovered by genotyping. Four patients died 23 - 64 days after onset of respiratory symptoms (23).

Moreira et al performed an epidemiological and methodological study of HRSV detection among children and patients with hematological malignancies receiving hematopoietic stem cell transplant (HSCT). In this study, 102 samples were collected from 67 HSCT recipients among whom there were 19 (28.8%) leukemia cases, 22 (33.3%) lymphoma cases and 25 (37.9%) cases with other hematological malignancies who had 4 (22.2%), 7 (38.9%) and 7 (38.9%) positive HRSV samples respectively (Table 1). Two separate episodes of HRSV occurred in one of these patients in 2008 (24). From January 16 to February 4, 2004, 6 RSV infected patients with hematological malignancies were admitted to an adult HSCT unit with the ages of 41, 26, 61, 62, 61 and 67 years who had cutaneous T cell lymphoma, nodular sclerosing Hodgkin disease, multiple myeloma, CML, mantle cell lymphoma and CML respectively, from which the second and the last (33%) developed URTI and other four patients (67%) developed HRSV-associated pneumonia. Two of these cases died due to the pneumonia (25).

In another study (Small et al. 1994 - 2001), 548 patients, who had received HSCT, were evaluated for HRSV infection. Among them 48 allogeneic HSCT patients had a positive result for HRSV infection by direct fluorescent antibody test (DFA), enzyme immunoassay (EIA) and Conventional cultures in rhesus monkey kidney cells, of whom 37

patients had hematological malignancies including CML and CLL (11 cases), acute leukemia (22 cases), lymphoma (3 cases) and multiple myeloma (1 case). In this study, twenty-five HRSV infected patients developed lower respiratory tract disease (LRTD) and pneumonia. Sixteen of them had hematological malignancies. Three patients died due to pneumonia (26). During eight consecutive winters 1992 - 2000, HRSV infection was investigated in 249 hospitalized women with breast cancer who had received autologous blood and marrow transplant. By means of ELISA, indirect immunofluorescence and cell cultures (Madin-Darby canine kidney cells, rhesus monkey kidney continuous cell line (LLC-MK2), human laryngeal tumor cells (Hep-2) and human embryonic lung fibroblasts (WI-38)), HRSV infection was detected in nine patients. Six of these patients developed pneumonia and two of them died due to the pneumonia (27).

The natural history of HRSV infection in cancer and transplant patients was studied by Anaissie *et al* from October 3, 1997 to October 14, 1998. Nasopharyngeal wash, BAL and lung biopsy samples were collected from 190 cancer patients with the median age of 58 years, prior to chemotherapy. 147 (77%) patients were considered as multiple myeloma (MM). Samples were cultured in tubes containing human diploid embryonic lung (MRC-5) fibroblast cells and were checked daily for the characteristic RSV cytopathic effect (CPE). Cultures with CPE were considered HRSV positive if they were confirmed by an indirect immunofluorescence test. Samples which had a negative culture but a positive IFA result also considered as positive. HRSV infection was totally positive in 56 of 147 MM patients of whom 6 (11%) developed pneumonia, 5 (9%) were transferred to intensive care unit (ICU) and 3 (5%) died within 30 days of therapy (28).

Other studies also have reported high incidence of HRSV in a variety of age groups. Roghmann *et al.* investigated respiratory viral infections (RVI) in 62 outpatient adults who had undergone SCT. 37 episodes of respiratory symptoms were observed in 35 (56%) patients. Nasopharyngeal aspirates were taken from each episode at the onset of respiratory symptoms and were subsequently tested for respiratory viruses using culture and RT-PCR. Viral respiratory tract infections were confirmed in 22 episodes. RSV was discovered in 9 episodes 6 of which developed URI and 3 remaining episodes led to LRI. Other viruses included Flu B, HPIV3, Flu A and picornavirus which resulted in 3, 5, 1 and 3 episodes, respectively. All of these episodes led to URI and just Flu B virus caused 2 LRI cases (29).

In another investigation by Benites *et al.* on acute RVI in pediatric cancer patients receiving chemotherapy, 104 children under 21 years of age suffering from different malignancies with dominancy of ALL and osteosar-

coma were examined for acute RVI. Collected nasopharyngeal aspirates were tested for RVI by rapid test (for influenza virus) and multiplex real-time PCR. Results showed that rhinovirus, RSV A and B, HMPV A and B, influenza B, coronavirus 229, coronavirus 43, influenza A, coronavirus 63, parainfluenza and influenza A/H1N1 were responsible for acute RVI (30). Clinical outcomes of HRSV infection also were studied among immunocompromised outpatient children with hematologic malignancy, solid organ transplant or hematopoietic cell transplant. The majority of HRSV infections ($n = 37$, 69%) were identified in hematologic malignant cases among which 16, 27, 24 and 2 cases showed fever, cough, rhinorrhea and wheezing, respectively which were higher compared to transplant recipients. Also one hematologic malignant patient was admitted to ICU due to HRSV infection (31).

3.2. Influenza Virus

Influenza viruses are respiratory pathogens from the family of orthomyxoviridae and genus Orthomyxovirus which are categorized into types A, B and C based on the variation in their nucleoprotein (NP) and M1 antigens (32, 33). Influenza viruses have a segmented negative-sense single stranded RNA genome (34). In Influenza A and B viruses, the genome contains eight segments of ssRNA but influenza C virus contains only seven segments of ssRNA (35, 36).

Influenza symptoms usually appear 1 to 3 days after being infected and often include: fever, dry cough, tiredness/extreme exhaustion, dyspnea, wheezing, headache, muscle and joint pain, sore throat and stuffy nose (37-39). Most people recover within a week but cough and tiredness may persist. Infected persons can disperse influenza to others one day before they become sick and 5 - 10 days after they become sick for adults and even longer for young children (40, 41). Influenza can escape from the human immune response due to rapid antigenic shift and drift (42). Because of this transient immunity, influenza can persist in small populations and sicken persons in all ages especially children younger than 2 years, adults older than 60 years, immunocompromised patients and pregnant women in whom the disease is more severe and fatal, and can develop severe pneumonia (43-46). Due to several genome rearrangements happening among influenza subtypes, infection by this virus has led to four pervasive pandemics (1918-1919 A(H1N1)-1957 A(H2N2)-1968 A(H3N2)-2009 A(H1N1)) (47-50).

In a cohort study by L. Souza *et al*, the pandemic H1N1 influenza A infection (2009) was investigated in 44 hospitalized cancer patients (median age 14.5, range 3 - 69 years) all of whom had an influenza-like illness. After screening

by indirect immunofluorescence and real-time RT-PCR, influenza infection was confirmed in 24 patients. Hematologic malignancy was observed in 18 (75%) of these patients, whereas solid tumors were observed in 6 (25%) patients. 13 (54%) patients were transferred to intensive care unit (ICU), 10 (41.6%) needed mechanical ventilation. The overall mortality in this study was about 21% (n = 5) (51). A group of scientists surveyed chest computed tomography (CT) scans in 8 influenza infected neutropenic cancer patients with fever and severe pneumonia. Respiratory failure was diagnosed in six (75%) of these patients and all of them were transferred to the intensive care unit (ICU). Four patients required invasive mechanical ventilation. From all patients, five developed pneumonia, two had CT scans indicating bronchitis and bronchiolitis, and others had signs of chronicity. Two patients died due to refractory hypoxia secondary to pulmonary alveolar hemorrhage and acute respiratory distress syndrome (ARDS) (52).

Tasian et al. performed a study on morbidity of influenza infection in children with cancer. The patients had various cancer types including acute lymphoblastic leukemia (10 patients), acute myelogenous leukemia (1 patient), Hodgkin lymphoma (1 patient), non-Hodgkin lymphoma (1 patient), Langerhans cell histiocytosis (2 patients), Wilms tumor (2 patients), osteosarcoma (2 patient), rhabdomyosarcoma (2 patients), neuroblastoma (3 patients), and brainstem glioma (1 patient). About 63% of these patients had lymphopenia. The infection was detected in Nasal wash specimens, BAL fluid, endotracheal tube aspirations, lung biopsies, and nasal swabs using direct fluorescent antibody (DFA) testing, viral culture and real time RT-PCR. Twenty-four influenza infected pediatric cancer patients (20 influenza A and 4 influenza B cases) with 27 clinical encounters were diagnosed. Two-thirds of patients were hospitalized due to severe respiratory symptoms. Primary influenza pneumonia occurred in three children. Mechanical ventilation was needed for 4 (15%) clinical encounters. Six patients had oxygen requirement for up to 30 days. No patients died during this study (53). In January 2011, a nosocomial outbreak of pandemic influenza A (H1N1pdm09) in hematologic patients was investigated for detection of oseltamivir resistant (OST-r) variants. 134 nasopharyngeal swabs, bronchoalveolar washes or respiratory secretions were collected from 76 hospitalized patients (age range: 23 - 76 years) and multiplex real time RT-PCR was done for matrix gene in order to distinguish influenzas A and B. Then influenza A positive samples were searched for H1N1pdm09 subtype using a fast real time PCR system and at last oseltamivir resistant variants were determined by means of RT-PCR and Sanger sequencing. Totally, 23 (30.2%) out of 76 patients were positive for H1N1pdm09 infection. Six of these patients with

ages 76, 50, 39, 42, 65 and 24 years were suffering from Non Hodgkin lymphoma, diffuse large cell Lymphoma, non Hodgkin lymphoma, acute myeloid leukemia, multiple myeloma and acute lymphoblastic leukemia respectively. Three of them developed acute respiratory distress syndrome and required intubation and mechanical ventilation, and eventually died because of fatal influenza pneumonia. Three patients were infected by OST-r variant (54). Redelman-Sidi et al. investigated this infection in cancer patients and hematopoietic stem cell transplant recipients. Nasopharyngeal swabs taken from 394 patients (age range of 3 - 80 years) were analyzed using DFA, culture in RMK cells and real time RT-PCR (for detection of viral load). The H1N1pdm09 was detected in 45 (11%) of these patients. 96 of 394 patients were HSCT recipients among whom 43 were with hematologic cancers and 16 were with solid tumors. 22% (n = 21) of the HSCT recipients were positive for H1N1pdm09 6 of whom developed LRTI. One patient with multiple myeloma was transferred to intensive care unit. No deaths occurred due to influenza infection (55). In a study GONZALEZ et al. searched for community respiratory virus infections (CRVI) in 224 BAL samples taken from 204 hematological malignant patients. CRVIs were detected in 21 cancer patients including 4 AML, 7 ALL, 6 non-Hodgkin's lymphoma, 2 Hodgkin's disease, 1 CLL and 1 neuroblastoma cases using culture in human fibroblasts (MRC5), human epithelial cells (Hep-2 and A-549) and Madin-Darby canine kidney cells (MDCK) cell lines and then were confirmed by immunofluorescence. Experiment results specified 8, 8, 3, 2 and 1 episodes of respiratory infections caused by influenza A virus, enterovirus, adenovirus, parainfluenza virus and rhinovirus, respectively. 15 cases of URTI occurred of which 5 were due to influenza, 5 were due to enterovirus, 2 were due to adenovirus, 2 were due to PIV and 1 was due to rhinovirus. Influenza A infection caused pneumonia in 7 patients and 4 of those led to death. Other 3 viruses, namely enterovirus, adenovirus and parainfluenza virus, were known as the cause of 6, 3 and 1 pneumonia cases respectively. Five patients died due to enteroviral pneumonia and two died because adenoviral pneumonia. No pneumonia or deaths were reported following rhinovirus infection (56).

Porter et al, reported several cases of RVI in 118 cancer patients (54 leukemia or lymphoma, 46 carcinoma and 18 sarcoma) who were died with malignant tumors. Autopsies taken from respiratory tract of all cases were examined by cell culture and Immunoenzyme staining. Viral antigens were found in 8 of all samples of which 5 were influenza A, one was influenza B, 2 were RSV and one was coinfecting by HPIV1 and CMV. Diffuse alveolar damage was observed in one influenza A case, one influenza B case, two RSV cases and the last coinfecting case. Clinical lung dis-

ease also was confirmed in all cases but one influenza case. Two deaths were due to diffuse alveolar damage and Pneumonia caused by influenza A. Respiratory failure by each of other detected viruses led to one death (57). In an epidemiology study of viral pneumonia in 38.5 - 70.5 year old adults, etiologic agents of pneumonia were identified by using FilmArray respiratory panel assay. Of the 284 adults with proven viral pneumonia, 95 (33.5%) had an active malignancy and the most frequent viral etiologies were influenza (24.3%), rhinovirus or enterovirus (23.6%), PIV (13%), and RSV (10.6%) (Table 1). The majority of patients with multiple viral infections had active malignancy. Fifty-eight of malignant patients were admitted to ICU following viral pneumonia (58). In another study, frequency of respiratory viral infections among children suffering from febrile neutropenia caused by cancer chemotherapy was surveyed by in-house real-time PCR. The most frequent viral infections were covering rhinovirus (n = 21, 24%), human Coronavirus (n = 7, 8%), influenza (n = 4, 5%), HRSV (n = 3, 3%), HPIV (n = 3, 3%), and HMPV (n = 2, 2%) (59).

3.3. Human Cytomegalovirus (HCMV)

Cytomegalovirus infection is known as an important cause of mental retardation in children and multi organ failure and lethal systemic infection among immunocompromised patients (60-63). CMV is classically located in cytomegalovirus genus from betaherpesvirinea subfamily of herpesviridea family. This virus is also known as human herpes virus 5 (HHV-5). The viral genome is a double stranded linear DNA which is encapsidated in an icosahedral capsid and a lipid bilayer envelope containing viral surface glycoproteins has covered this nucleocapsid. (64). The viral capsid proteins include MCP, CAP, TRI2, and SCP. Major tegument proteins consist of pp65, RRI, pp150, LTP, pp71 and VPK. The most important envelope glycoprotein is gB protein which mediates attachment to heparin sulfate and assists with gH and gL proteins in fusion with host cell membrane (65-73).

CMV infection should be considered as a causative agent of pneumonia in non-transplanted cancer patients, particularly if steroids are a component of their therapy. A study was performed on diagnosis and treatment of pulmonary opportunistic infections (Pneumocystis carini and CMV) in hematological malignant patients. These infections were discovered in sputum and lung biopsy samples collected from a total of 58 malignant patients by PCR, of which 7 (12.1%) cases were positive for Pc and 5 (8.6%) for CMV all of whom developed pneumonia. Totally 12 patients died because of respiratory failure. 6 of these were due to CMV (4 cases) and mucor pneumonia (2 cases), and the remaining 6 deaths were due to underlying malignant diseases. In 7 PCR positive Pc infected patients, early treat-

ment was effective in all of them and the deaths occurred following this infection were due to pathologic effects of CMV and mucor mycosis (one case with CMV only and one case with CMV and mucor coinfection). For CMV despite antiviral therapy, 3 of 5 PCR positive patients died from pneumonia. In addition, the level of fungal β -glucan in blood indicated mycotic pneumonia in nine of all patients and the treatment was effective in 7 of them (74). Chang et al. reported a case series of CMV infection in non-transplant patients (age range: 29 - 86) with hematologic malignancies. Serum and biopsy samples were collected from these patients. Then using clinical symptoms, radiographic results and laboratory tests, 20 episodes of infection were examined in 17 patients overtaken blood malignancies. Laboratory methods included histopathology, immunofluorescence, enzyme immunoassay and shell vial culture, which were used for detection of CMV inclusion bodies, pp65 antigens, CMV specific IgM or IgG in serum and shedding in BAL fluid, respectively. CMV infection occurred in 12 of 20 episodes. 10 patients had a positive CMV antigen assay. 7 patients developed pneumonia caused by CMV-D subtype and also their BAL samples resulted in positive culture. Among 17 patients, 6 survived within a 4 - 14 month follow up, one patient lost to follow up, and the remaining 10 patients died within a < 1 - 27 month period when CMV-D was the causative agent of two deaths. One death was due to CMV pneumonia (75).

3.4. Human Metapneumovirus (HMPV)

A considerable part of lower respiratory tract failures caused by viruses can be attributed to human metapneumovirus (HMPV). This virus is a member of metapneumovirus genus from pneumovirinea subfamily from paramixoviridea family and this family is a subset of the mononegavirals order. HMPV is a pleomorphic virus which is 150 - 600 nm in diameter. HMPV, like other members of paramixoviridea, contains a single stranded negative-sense RNA molecule. The gene order of virus (from 3' to 5') is N(nucleoprotein)- P(phosphoprotein)- M (matrix protein)- F (fusion protein)- M2(cods for M2-1 and M2-2)- SH(small hydrophobic protein)- G(attachment protein)- L(viral polymerase) (76-78).

Seroprevalence of HMPV among children with the age of 5 years is almost 100%. In a study by Walsh et al, the proportion of HMPV infection was between 3% - 7.1% in adult individuals (79). In this study HMPV infection was associated with hospitalization because of acute RTI and the incidence of infection in the hospitalized patients was 4.3% - 13.2% (80). In another study by widmer et al. the rate of hospitalization due to HMPV acute RTI was 4.5%. From the clinical aspect, most patients admitted with cough, nasal congestion and dyspnea. More severe symptoms include

purulent cough, wheezing, fever, sore throat, bronchitis, bronchiolitis, pneumonia, conjunctivitis and otitis media (81).

HMPV has been reported as a prevalent cause of respiratory failure among cancer patients. Williams et al. (1999 - 2004) compared this infection with other respiratory viral infections in adults with hematological malignancy (age range: 20 - 72). Nasopharyngeal aspirations and BAL samples from 251 episodes of respiratory infection in 128 malignant patients were surveyed for viral etiologies using direct immunofluorescence assays (DFA), cultured in LLC-MK2 cells and RT-PCR. Among 22 patients who tested positive for HMPV, 20 had URTI, 9 developed LRTI as pneumonia which led to 3 deaths. The number of pneumonia caused by other detected infections including influenza, RSV, PIV1&3, adenovirus, rhinovirus and enterovirus was 20, 11, 6, 5, 0 and 2 cases and the number of deaths which occurred due to the first four infections was 4, 3, 2 and 2 cases and no deaths were associated with latter two infections (82). In another study, data acquired from analyzing 2795 nasopharyngeal swabs and bronchoscopy specimens of 2125 patients with solid tumors, leukemia, lymphoma and other hematological disorders were investigated for HMPV infection. Applied laboratory methods included DFA and real-time PCR. HMPV infection was diagnosed in 51 patients. No severe respiratory symptoms were caused by HMPV but one patient died due to coinfection with RSV and toxoplasma (83).

3.5. Human Parainfluenza Virus (HPIV)

Human parainfluenza virus (HPIV) is a prevalent cause of upper and lower respiratory failure chiefly in infants and young children (84). There were more than 5 million LRI cases each year during 1980 - 86 in the United States in children younger than 5 years. HPIVs 1 - 3 had been identified in about one-third of these infections (85-87). Most children with the age of 6 - 10 years have evidence of past infection (92). 3% - 18% of all admissions to pediatric hospitals are due to acute respiratory infections (ARTI) and HPIV infection was detected in 9% - 30% of these patients (87-89). LRI causes 25 to 30% of deaths in childhood and HPIV causes at least 10% of these LRIs. Mortality caused by HPIV often is seen in young infants, immunocompromised patients and the elderly (1).

In a study by Lewis et al. (1991 - 1994) the rates of developing parainfluenza pneumonia and mortality among bone marrow transplant (BMT) recipients were 44% and 37%, respectively (90). HPIV infection usually causes otitis media, pharyngitis, conjunctivitis, and coryza. More severe symptoms include croup (acute laryngotracheobronchitis), Tracheobronchitis, Bronchiolitis, pneumonia and Neurologic diseases (89, 91-94).

In terms of classification, this virus is a member of mononegavirals order, paramixoviridea family and subfamily of paramixovirinea. Four types (1, 2, 3 and 4) are determined for HPIV. The type 4 is subdivided to 4A and 4B subtypes. The types 1 and 3 fall into respirovirus genus but types 2 and 4 are categorized in rubulavirus genus. This virus is a pleomorphic virus that is 150 - 250 nm in diameter with a lipid envelope covering helical nucleocapsid (91-94).

In a retrospective study, the data recorded between January 2000 and July 2008 from 1554 pediatric cancer patients were examined for consequences of HPIV infection. BAL and tracheal aspiration samples were taken from the patients and then tested by direct fluorescent antibody assay DFA, rapid antigen tests and cell culture method. 137 (6.4%) of all patients were overtaken a viral respiratory infection who 74 (54%) of them were infected by HPIV. HPIV3 was the dominant subtype among the patients. 59 (79.7%) of HPIV infected children had upper respiratory tract infection (URTI) while 15 (20.3%) of them had lower respiratory tract infection (LRTI). 12 of URTI cases had developed pneumonia subsequently. 59 of HPIV infections were nosocomial cases. 5 of 27 LRTI cases finally died due to respiratory failure (4 due to ARDS and one due to pulmonary hemorrhage) (95).

Srinivasan et al. (2000 - 2009) performed another retrospective study on HPIV infection in 820 hematological malignant children. Nasopharyngeal swab and wash samples were taken from patients. By infection of rhesus monkey kidney, A549 and MDCK cell lines and using DFA staining and real-time PCR, HPIV infection was confirmed in 83 (10%) of all patients the majority of whom were < 2 years old and suffering from ALL. HPIV1-4 subtypes also were distinguished on the basis of hemadsorption outcomes. URTI was diagnosed in 66 (80%) of infected patients and the remaining 17 patients developed LRTI. Despite mechanical ventilation requirement in 3 children, none of them died due to respiratory failure (96). Chemaly et al. in their research diagnosed HPIV infection in 200 patients including 80 leukemia cases and 120 hematopoietic stem cell transplant (HSCT) recipients. Most frequent malignancies were Acute myeloid leukemia (44%) and acute lymphoblastic leukemia (28%). 70% of patients had URTI and the remaining 30% had developed pneumonia at the time of admission. Among leukemia patients, 10 were transferred to ICU due to severe pneumonia and 8 of them needed mechanical ventilation all of whom died of respiratory failure. For HSCT recipients, the rates of transmission to ICU, mechanical ventilation requirement and death due to pneumonia were 7, 5 and 8 cases, respectively (97).

4. Conclusions

In summary, viral respiratory infection is caused by HRSV, influenza virus, HCMV, HMPV and HPIV is prevalent in patients with cancer. These infections can worsen the patient's condition and disrupt the treatment process. On the other hand, viral respiratory infection easily spread in the hospital parts and control of these infections is difficult. Therefore, prevention and treatment of respiratory viral infections in cancer patients is of great importance.

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Footnotes

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References

- Berman S. Epidemiology of acute respiratory infections in children of developing countries. *Rev Infect Dis.* 1991;**13 Suppl 6**:S454-62. [PubMed: 1862276].
- Falsey AR, Walsh EE. Respiratory syncytial virus infection in adults. *Clin Microbiol Rev.* 2000;**13**(3):371-84. [PubMed: 10885982].
- Walsh EE, Peterson DR, Falsey AR. Risk factors for severe respiratory syncytial virus infection in elderly persons. *J Infect Dis.* 2004;**189**(2):233-8. doi: 10.1086/380907. [PubMed: 14722887].
- Dawson-Caswell M, Muncie HL Jr. Respiratory syncytial virus infection in children. *Am Fam Physician.* 2011;**83**(2):141-6. [PubMed: 21243988].
- Holman RC, Curns AT, Cheek JE, Bresee JS, Singleton RJ, Carver K, et al. Respiratory syncytial virus hospitalizations among American Indian and Alaska Native infants and the general United States infant population. *Pediatrics.* 2004;**114**(4):e437-44. doi: 10.1542/peds.2004-0049. [PubMed: 15466069].
- Romano F, Uggeri F, Crippa S, Di Stefano G, Scotti M, Scaini A, et al. Immunodeficiency in different histotypes of radically operable gastrointestinal cancers. *J Exp Clin Cancer Res.* 2004;**23**(2):195-200. [PubMed: 15354402].
- Silva FA, Matos JO, de QF, Nucci M. Risk factors for and attributable mortality from tuberculosis in patients with hematologic malignancies. *Haematologica.* 2005;**90**(8):1110-5. [PubMed: 16079111].
- Chang M, Wu L, Lu T. Topics in Cancer Survivorship. Ravinder Mohan: InTech; 2012.
- Li Y. T-cell immunodeficiency and reconstruction based on TCR rearrangement analysis in hematological malignancy: update from 2011 ASH annual meeting. *J Hematol Oncol.* 2012;**5**(Suppl 1):A3. doi: 10.1186/1756-8722-5-s1-a3.
- Hamblin AD, Hamblin TJ. The immunodeficiency of chronic lymphocytic leukaemia. *Br Med Bull.* 2008;**87**:49-62. doi: 10.1093/bmb/ldn034. [PubMed: 18755702].
- Speer ME, Good AB. The prevention of respiratory syncytial virus infection in children: focus on palivizumab. *Clin Med Insights Ther.* 2009;**1**:459.
- Ghildyal R, Ho A, Jans DA. Central role of the respiratory syncytial virus matrix protein in infection. *FEMS Microbiol Rev.* 2006;**30**(5):692-705. doi: 10.1111/j.1574-6976.2006.00025.x. [PubMed: 16911040].
- Rodriguez L, Cuesta I, Asenjo A, Villanueva N. Human respiratory syncytial virus matrix protein is an RNA-binding protein: binding properties, location and identity of the RNA contact residues. *J Gen Virol.* 2004;**85**(Pt 3):709-19. doi: 10.1099/vir.0.19707-0. [PubMed: 14993657].
- Ulloa L, Serra R, Asenjo A, Villanueva N. Interactions between cellular actin and human respiratory syncytial virus (HRSV). *Virus Res.* 1998;**53**(1):13-25. [PubMed: 9617766].
- Hacimustafaoglu M, Celebi S, Bozdemir SE, Ozgur T, Ozcan I, Guray A, et al. RSV frequency in children below 2 years hospitalized for lower respiratory tract infections. *Turk J Pediatr.* 2013;**55**(2):130-9. [PubMed: 24192672].
- Shay DK, Holman RC, Newman RD, Liu LL, Stout JW, Anderson LJ. Bronchiolitis-associated hospitalizations among US children, 1980-1996. *JAMA.* 1999;**282**(15):1440-6. [PubMed: 10535434].
- Nair H, Nokes DJ, Gessner BD, Dherani M, Madhi SA, Singleton RJ, et al. Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: a systematic review and meta-analysis. *Lancet.* 2010;**375**(9725):1545-55. doi: 10.1016/S0140-6736(10)60206-1. [PubMed: 20399493].
- Faghiloo E, Salimi V, Rezaei F, Naseri M, Mamishi S, Mahmoodi M, et al. Genetic Diversity in the G Protein Gene of Human Respiratory Syncytial Virus among Iranian Children with Acute Respiratory Symptoms. *Iran J Pediatr.* 2011;**21**(1):58-64. [PubMed: 23056765].
- Faghiloo E, Rezaei F, Salimi V, Naseri M, Mamishi S, Mahmoodi M, et al. Molecular epidemiology of human respiratory syncytial virus in Iran. *Acta Virol.* 2011;**55**(1):81-3. [PubMed: 21434709].
- Faghiloo E, Yavarian J, Jandaghi NZ, Shadab A, Azad TM. Genotype circulation pattern of human respiratory syncytial virus in Iran. *Infect Genet Evol.* 2014;**22**:130-3. doi: 10.1016/j.meegid.2014.01.009. [PubMed: 24462624].
- Torres HA, Aguilera EA, Mattiuzzi GN, Cabanillas ME, Rohatgi N, Sepulveda CA, et al. Characteristics and outcome of respiratory syncytial virus infection in patients with leukemia. *Haematologica.* 2007;**92**(9):1216-23. [PubMed: 17666367].
- Salter A, Laoi BN, Crowley B. Molecular epidemiology of human respiratory syncytial virus subgroups A and B identified in adults with hematological malignancy attending an Irish hospital between 2004 and 2009. *J Med Virol.* 2011;**83**(2):337-47. doi: 10.1002/jmv.21957. [PubMed: 21181932].
- Mazzulli T, Peret TC, McGeer A, Cann D, MacDonald KS, Chua R, et al. Molecular characterization of a nosocomial outbreak of human respiratory syncytial virus on an adult leukemia/lymphoma ward. *J Infect Dis.* 1999;**180**(5):1686-9. doi: 10.1086/315085. [PubMed: 10515833].
- Moreira LP, Watanabe AS, Carraro E, da Silva ER, Guatura SB, Granato C, et al. A survey strategy for human respiratory syncytial virus detection among haematopoietic stem cell transplant patients: epidemiological and methodological analysis. *Mem Inst Oswaldo Cruz.* 2013;**108**(1):119-22. [PubMed: 23440127].
- Kassis C, Champlin RE, Hachem RY, Hosing C, Tarrand JJ, Perego CA, et al. Detection and control of a nosocomial respiratory syncytial virus outbreak in a stem cell transplantation unit: the role of palivizumab. *Biol Blood Marrow Transplant.* 2010;**16**(9):1265-71. doi: 10.1016/j.bbmt.2010.03.011. [PubMed: 20304082].
- Small TN, Casson A, Malak SF, Boulad F, Kiehn TE, Stiles J, et al. Respiratory syncytial virus infection following hematopoietic stem cell transplantation. *Bone Marrow Transplant.* 2002;**29**(4):321-7. doi: 10.1038/sj.bmt.1703365. [PubMed: 11896429].
- Ghosh S, Champlin RE, Ueno NT, Anderlini P, Rolston K, Raad I, et al. Respiratory syncytial virus infections in autologous blood and marrow transplant recipients with breast cancer: combination therapy with aerosolized ribavirin and parenteral immunoglobulins. *Bone Marrow Transplant.* 2001;**28**(3):271-5. doi: 10.1038/sj.bmt.1703131. [PubMed: 11535995].

28. Anaissie EJ, Mahfouz TH, Aslan T, Pouli A, Desikan R, Fassas A, et al. The natural history of respiratory syncytial virus infection in cancer and transplant patients: implications for management. *Blood*. 2004;**103**(5):1611-7. doi: [10.1182/blood-2003-05-1425](https://doi.org/10.1182/blood-2003-05-1425). [PubMed: [14525792](https://pubmed.ncbi.nlm.nih.gov/14525792/)].
29. Roghmann M, Ball K, Erdman D, Lovchik J, Anderson LJ, Edelman R. Active surveillance for respiratory virus infections in adults who have undergone bone marrow and peripheral blood stem cell transplantation. *Bone Marrow Transplant*. 2003;**32**(11):1085-8. doi: [10.1038/sj.bmt.1704257](https://doi.org/10.1038/sj.bmt.1704257). [PubMed: [14625580](https://pubmed.ncbi.nlm.nih.gov/14625580/)].
30. Benites EC, Cabrini DP, Silva AC, Silva JC, Catalan DT, Berezin EN, et al. Acute respiratory viral infections in pediatric cancer patients undergoing chemotherapy. *J Pediatr (Rio J)*. 2014;**90**(4):370-6. doi: [10.1016/j.jpeds.2014.01.006](https://doi.org/10.1016/j.jpeds.2014.01.006). [PubMed: [24703819](https://pubmed.ncbi.nlm.nih.gov/24703819/)].
31. Chu HY, Chin J, Pollard J, Zerr DM, Englund JA. Clinical outcomes in outpatient respiratory syncytial virus infection in immunocompromised children. *Influenza Other Respir Viruses*. 2016;**10**(3):205-10. doi: [10.1111/irv.12375](https://doi.org/10.1111/irv.12375). [PubMed: [26859306](https://pubmed.ncbi.nlm.nih.gov/26859306/)].
32. Hampson AW, Mackenzie JS. The influenza viruses. *Med J Aust*. 2006;**185**(10 Suppl):S39-43. [PubMed: [17115950](https://pubmed.ncbi.nlm.nih.gov/17115950/)].
33. Tobita K. [Classification and nomenclature of influenza viruses]. *Nihon Rinsho*. 1997;**55**(10):2512-4. [PubMed: [9360365](https://pubmed.ncbi.nlm.nih.gov/9360365/)].
34. Noda T. Native morphology of influenza virions. *Front Microbiol*. 2011;**2**:269. doi: [10.3389/fmicb.2011.00269](https://doi.org/10.3389/fmicb.2011.00269). [PubMed: [22291683](https://pubmed.ncbi.nlm.nih.gov/22291683/)].
35. Nakajima K. [Influenza virus genome structure and encoded proteins]. *Nihon Rinsho*. 1997;**55**(10):2542-6. [PubMed: [9360369](https://pubmed.ncbi.nlm.nih.gov/9360369/)].
36. Cheung TK, Poon LL. Biology of influenza A virus. *Ann N Y Acad Sci*. 2007;**1102**:1-25. doi: [10.1196/annals.1408.001](https://doi.org/10.1196/annals.1408.001). [PubMed: [17470908](https://pubmed.ncbi.nlm.nih.gov/17470908/)].
37. Hajjar LA, Mauad T, Galas FR, Kumar A, da Silva LF, Dolhnikoff M, et al. Severe novel influenza A (H1N1) infection in cancer patients. *Ann Oncol*. 2010;**21**(12):2333-41. doi: [10.1093/annonc/mdq254](https://doi.org/10.1093/annonc/mdq254). [PubMed: [20511340](https://pubmed.ncbi.nlm.nih.gov/20511340/)].
38. Kondo K. Post-infectious fatigue. *Japan Med Assoc J*. 2006;**49**(1):27.
39. Amayiri N, Madanat F. Retrospective analysis of pediatric cancer patients diagnosed with the pandemic H1N1 influenza infection. *Pediatr Blood Cancer*. 2011;**56**(1):86-9. doi: [10.1002/pbc.22805](https://doi.org/10.1002/pbc.22805). [PubMed: [21108443](https://pubmed.ncbi.nlm.nih.gov/21108443/)].
40. Carrat F, Vergu E, Ferguson NM, Lemaître M, Cauchemez S, Leach S, et al. Time lines of infection and disease in human influenza: a review of volunteer challenge studies. *Am J Epidemiol*. 2008;**167**(7):775-85. doi: [10.1093/aje/kwm375](https://doi.org/10.1093/aje/kwm375). [PubMed: [18230677](https://pubmed.ncbi.nlm.nih.gov/18230677/)].
41. Hayden FG, Fritz R, Lobo MC, Alvord W, Strober W, Straus SE. Local and systemic cytokine responses during experimental human influenza A virus infection. Relation to symptom formation and host defense. *J Clin Invest*. 1998;**101**(3):643-9. doi: [10.1172/JCI1355](https://doi.org/10.1172/JCI1355). [PubMed: [9449698](https://pubmed.ncbi.nlm.nih.gov/9449698/)].
42. Treanor J. Influenza vaccine-outmaneuvering antigenic shift and drift. *N Engl J Med*. 2004;**350**(3):218-20. doi: [10.1056/NEJMp038238](https://doi.org/10.1056/NEJMp038238). [PubMed: [14724300](https://pubmed.ncbi.nlm.nih.gov/14724300/)].
43. Monto AS, Kioumehrf F. The Tecumseh Study of Respiratory Illness. IX. Occurrence of influenza in the community, 1966-1971. *Am J Epidemiol*. 1975;**102**(6):553-63. [PubMed: [1202957](https://pubmed.ncbi.nlm.nih.gov/1202957/)].
44. Glezen WP, Couch RB. Interpandemic influenza in the Houston area, 1974-76. *N Engl J Med*. 1978;**298**(11):587-92. doi: [10.1056/NEJM197803162981103](https://doi.org/10.1056/NEJM197803162981103). [PubMed: [628375](https://pubmed.ncbi.nlm.nih.gov/628375/)].
45. Thompson WW, Shay DK, Weintraub E, Brammer L, Bridges CB, Cox NJ, et al. Influenza-associated hospitalizations in the United States. *JAMA*. 2004;**292**(11):1333-40. doi: [10.1001/jama.292.11.1333](https://doi.org/10.1001/jama.292.11.1333). [PubMed: [15367555](https://pubmed.ncbi.nlm.nih.gov/15367555/)].
46. Keren R, Zaoutis TE, Bridges CB, Herrera G, Watson BM, Wheeler AB, et al. Neurological and neuromuscular disease as a risk factor for respiratory failure in children hospitalized with influenza infection. *JAMA*. 2005;**294**(17):2188-94. doi: [10.1001/jama.294.17.2188](https://doi.org/10.1001/jama.294.17.2188). [PubMed: [16264160](https://pubmed.ncbi.nlm.nih.gov/16264160/)].
47. Johnson NP, Mueller J. Updating the accounts: global mortality of the 1918-1920 "Spanish" influenza pandemic. *Bull Hist Med*. 2002;**76**(1):105-15. [PubMed: [11875246](https://pubmed.ncbi.nlm.nih.gov/11875246/)].
48. Bull Org Mond Sante. *Influenza*. 20. ;1959.
49. Bull Org Mond Sante. *Influenza*. 41. ;1969. pp. 335-748.
50. Antoine Flahault MD. Influenza pandemics: past, present and future challenges. *Public Health Rev*. 2010;**32**(1):319-40.
51. Souza TM, Salluh JI, Bozza FA, Mesquita M, Soares M, Motta FC, et al. H1N1pdm influenza infection in hospitalized cancer patients: clinical evolution and viral analysis. *PLoS One*. 2010;**5**(11):e14158. doi: [10.1371/journal.pone.0014158](https://doi.org/10.1371/journal.pone.0014158). [PubMed: [21152402](https://pubmed.ncbi.nlm.nih.gov/21152402/)].
52. Rodrigues RS, Marchiori E, Bozza FA, Pitrowsky MT, Velasco E, Soares M, et al. Chest computed tomography findings in severe influenza pneumonia occurring in neutropenic cancer patients. *Clinics (Sao Paulo)*. 2012;**67**(4):313-8. [PubMed: [22522755](https://pubmed.ncbi.nlm.nih.gov/22522755/)].
53. Tasian SK, Park JR, Martin ET, Englund JA. Influenza-associated morbidity in children with cancer. *Pediatr Blood Cancer*. 2008;**50**(5):983-7. doi: [10.1002/pbc.21472](https://doi.org/10.1002/pbc.21472). [PubMed: [18240170](https://pubmed.ncbi.nlm.nih.gov/18240170/)].
54. Pollara CP, Piccinelli G, Rossi G, Cattaneo C, Perandin F, Corbellini S, et al. Nosocomial outbreak of the pandemic Influenza A (H1N1) 2009 in critical hematologic patients during seasonal influenza 2010-2011: detection of oseltamivir resistant variant viruses. *BMC Infect Dis*. 2013;**13**:127. doi: [10.1186/1471-2334-13-127](https://doi.org/10.1186/1471-2334-13-127). [PubMed: [23496867](https://pubmed.ncbi.nlm.nih.gov/23496867/)].
55. Redelman-Sidi G, Sepkowitz KA, Huang CK, Park S, Stiles J, Eagan J, et al. 2009 H1N1 influenza infection in cancer patients and hematopoietic stem cell transplant recipients. *J Infect*. 2010;**60**(4):257-63. doi: [10.1016/j.jinf.2010.01.009](https://doi.org/10.1016/j.jinf.2010.01.009). [PubMed: [20138188](https://pubmed.ncbi.nlm.nih.gov/20138188/)].
56. Gonzalez Y, Martino R, Rabella N, Labeaga R, Badell I, Sierra J. Community respiratory virus infections in patients with hematologic malignancies. *Haematologica*. 1999;**84**(9):820-3. [PubMed: [10477456](https://pubmed.ncbi.nlm.nih.gov/10477456/)].
57. Porter DD, Porter HG. Respiratory viral antigens in autopsy lung tissue specimens from patients with cancer or myocardial infarction. *Clin Infect Dis*. 1999;**29**(2):437-40. doi: [10.1086/520230](https://doi.org/10.1086/520230). [PubMed: [10476756](https://pubmed.ncbi.nlm.nih.gov/10476756/)].
58. Crotty MP, Meyers S, Hampton N, Bledsoe S, Ritchie DJ, Buller RS, et al. Epidemiology, Co-Infections, and Outcomes of Viral Pneumonia in Adults: An Observational Cohort Study. *Medicine (Baltimore)*. 2015;**94**(50):e2332. doi: [10.1097/MD.0000000000002332](https://doi.org/10.1097/MD.0000000000002332). [PubMed: [26683973](https://pubmed.ncbi.nlm.nih.gov/26683973/)].
59. Soderman M, Rhedin S, Tolfvenstam T, Rotzen-Ostlund M, Albert J, Broliden K, et al. Frequent Respiratory Viral Infections in Children with Febrile Neutropenia - A Prospective Follow-Up Study. *PLoS One*. 2016;**11**(6):e0157398. doi: [10.1371/journal.pone.0157398](https://doi.org/10.1371/journal.pone.0157398). [PubMed: [27309354](https://pubmed.ncbi.nlm.nih.gov/27309354/)].
60. Gandhoke I, Aggarwal R, Lal S, Khare S. Congenital CMV infection in symptomatic infants in Delhi and surrounding areas. *Indian J Pediatr*. 2006;**73**(12):1095-7. [PubMed: [17202637](https://pubmed.ncbi.nlm.nih.gov/17202637/)].
61. Munro SC, Trincado D, Hall B, Rawlinson WD. Symptomatic infant characteristics of congenital cytomegalovirus disease in Australia. *J Paediatr Child Health*. 2005;**41**(8):449-52. doi: [10.1111/j.1440-1754.2005.00665.x](https://doi.org/10.1111/j.1440-1754.2005.00665.x). [PubMed: [16101982](https://pubmed.ncbi.nlm.nih.gov/16101982/)].
62. Istan AS, Demmler GJ, Dobbins JG, Stewart JA. Surveillance for congenital cytomegalovirus disease: a report from the National Congenital Cytomegalovirus Disease Registry. *Clin Infect Dis*. 1995;**20**(3):665-70. [PubMed: [7756493](https://pubmed.ncbi.nlm.nih.gov/7756493/)].
63. Pannuti CS, Vilas Boas LS, Angelo MJ, Amato Neto V, Levi GC, de Mendonca JS, et al. Cytomegalovirus mononucleosis in children and adults: differences in clinical presentation. *Scand J Infect Dis*. 1985;**17**(2):153-6. [PubMed: [2992073](https://pubmed.ncbi.nlm.nih.gov/2992073/)].
64. Landolfo S, Gariglio M, Gribaudo G, Lembo D. The human cytomegalovirus. *Pharmacol Ther*. 2003;**98**(3):269-97. doi: [10.1016/s0163-7258\(03\)00034-2](https://doi.org/10.1016/s0163-7258(03)00034-2).
65. Britt B. In: Human Herpesviruses: Biology, Therapy and Immunoprophylaxis. Arvin A, Campadelli-F G, Mocarski E, Moore PS, Roizman B, Whitley R, et al, editors. Cambridge: Cambridge Press; 2007. pp. 311-23. CMV maturation and egress.
66. Kagele D, Gao Y, Smallenburg K, Pari GS. Interaction of HCMV UL84 with C/EBPalpha transcription factor binding sites within oriLyt is

- essential for lytic DNA replication. *Virology*. 2009;**392**(1):16–23. doi: [10.1016/j.virol.2009.06.035](https://doi.org/10.1016/j.virol.2009.06.035). [PubMed: [19631360](https://pubmed.ncbi.nlm.nih.gov/19631360/)].
67. Kim YE, Ahn JH. Role of the specific interaction of UL112-113 p84 with UL44 DNA polymerase processivity factor in promoting DNA replication of human cytomegalovirus. *J Virol*. 2010;**84**(17):8409–21. doi: [10.1128/JVI.00189-10](https://doi.org/10.1128/JVI.00189-10). [PubMed: [20538862](https://pubmed.ncbi.nlm.nih.gov/20538862/)].
 68. Li R, Zhu J, Xie Z, Liao G, Liu J, Chen MR, et al. Conserved herpesvirus kinases target the DNA damage response pathway and TIP60 histone acetyltransferase to promote virus replication. *Cell Host Microbe*. 2011;**10**(4):390–400. doi: [10.1016/j.chom.2011.08.013](https://doi.org/10.1016/j.chom.2011.08.013). [PubMed: [22018239](https://pubmed.ncbi.nlm.nih.gov/22018239/)].
 69. Prichard MN. Function of human cytomegalovirus UL97 kinase in viral infection and its inhibition by maribavir. *Rev Med Virol*. 2009;**19**(4):215–29. doi: [10.1002/rmv.615](https://doi.org/10.1002/rmv.615). [PubMed: [19434630](https://pubmed.ncbi.nlm.nih.gov/19434630/)].
 70. Reeves M, Woodhall D, Compton T, Sinclair J. Human cytomegalovirus IE72 protein interacts with the transcriptional repressor hDaxx to regulate LUNA gene expression during lytic infection. *J Virol*. 2010;**84**(14):7185–94. doi: [10.1128/JVI.02231-09](https://doi.org/10.1128/JVI.02231-09). [PubMed: [20444888](https://pubmed.ncbi.nlm.nih.gov/20444888/)].
 71. Stanton RJ, Baluchova K, Dargan DJ, Cunningham C, Sheehy O, Seirafian S, et al. Reconstruction of the complete human cytomegalovirus genome in a BAC reveals RL13 to be a potent inhibitor of replication. *J Clin Invest*. 2010;**120**(9):3191–208. doi: [10.1172/JCI42955](https://doi.org/10.1172/JCI42955). [PubMed: [20679731](https://pubmed.ncbi.nlm.nih.gov/20679731/)].
 72. Tandon R, Mocarski ES. Control of cytoplasmic maturation events by cytomegalovirus tegument protein pp150. *J Virol*. 2008;**82**(19):9433–44. doi: [10.1128/JVI.00533-08](https://doi.org/10.1128/JVI.00533-08). [PubMed: [18653449](https://pubmed.ncbi.nlm.nih.gov/18653449/)].
 73. Yu X, Shah S, Lee M, Dai W, Lo P, Britt W, et al. Biochemical and structural characterization of the capsid-bound tegument proteins of human cytomegalovirus. *J Struct Biol*. 2011;**174**(3):451–60. doi: [10.1016/j.jsb.2011.03.006](https://doi.org/10.1016/j.jsb.2011.03.006). [PubMed: [21459145](https://pubmed.ncbi.nlm.nih.gov/21459145/)].
 74. Jojima H. Early diagnosis and treatment of pulmonary opportunistic infection by using polymerase chain reaction and beta-glucan in patients with hematological neoplasms. *Kurume Med J*. 2001;**48**(2):117–27. [PubMed: [11501492](https://pubmed.ncbi.nlm.nih.gov/11501492/)].
 75. Chang H, Tang TC, Hung YS, Lin TL, Kuo MC, Wang PN. Cytomegalovirus infection in non-transplant patients with hematologic neoplasms: a case series. *Chang Gung Med J*. 2011;**34**(1):65–74. [PubMed: [21392476](https://pubmed.ncbi.nlm.nih.gov/21392476/)].
 76. Haas LE, Thijsen SF, van Elden L, Heemstra KA. Human metapneumovirus in adults. *Viruses*. 2013;**5**(1):87–110. doi: [10.3390/v5010087](https://doi.org/10.3390/v5010087). [PubMed: [23299785](https://pubmed.ncbi.nlm.nih.gov/23299785/)].
 77. Panda S, Mohakud NK, Pena L, Kumar S. Human metapneumovirus: review of an important respiratory pathogen. *Int J Infect Dis*. 2014;**25**:45–52. doi: [10.1016/j.ijid.2014.03.1394](https://doi.org/10.1016/j.ijid.2014.03.1394). [PubMed: [24841931](https://pubmed.ncbi.nlm.nih.gov/24841931/)].
 78. Kahn JS. Epidemiology of human metapneumovirus. *Clin Microbiol Rev*. 2006;**19**(3):546–57. doi: [10.1128/CMR.00014-06](https://doi.org/10.1128/CMR.00014-06). [PubMed: [16847085](https://pubmed.ncbi.nlm.nih.gov/16847085/)].
 79. Walsh EE, Peterson DR, Falsey AR. Human metapneumovirus infections in adults: another piece of the puzzle. *Arch Intern Med*. 2008;**168**(22):2489–96. doi: [10.1001/archinte.168.22.2489](https://doi.org/10.1001/archinte.168.22.2489). [PubMed: [19064834](https://pubmed.ncbi.nlm.nih.gov/19064834/)].
 80. Falsey AR. Respiratory syncytial virus infection in elderly and high-risk adults. *Exp Lung Res*. 2005;**31** Suppl 1:77. [PubMed: [16395866](https://pubmed.ncbi.nlm.nih.gov/16395866/)].
 81. Widmer K, Zhu Y, Williams JV, Griffin MR, Edwards KM, Talbot HK. Rates of hospitalizations for respiratory syncytial virus, human metapneumovirus, and influenza virus in older adults. *J Infect Dis*. 2012;**206**(1):56–62. doi: [10.1093/infdis/jis309](https://doi.org/10.1093/infdis/jis309). [PubMed: [22529314](https://pubmed.ncbi.nlm.nih.gov/22529314/)].
 82. Williams JV, Martino R, Rabella N, Otegui M, Parody R, Heck JM, et al. A prospective study comparing human metapneumovirus with other respiratory viruses in adults with hematologic malignancies and respiratory tract infections. *J Infect Dis*. 2005;**192**(6):1061–5. doi: [10.1086/432732](https://doi.org/10.1086/432732). [PubMed: [16107960](https://pubmed.ncbi.nlm.nih.gov/16107960/)].
 83. Kamboj M, Gerbin M, Huang CK, Brennan C, Stiles J, Balashov S, et al. Clinical characterization of human metapneumovirus infection among patients with cancer. *J Infect*. 2008;**57**(6):464–71. doi: [10.1016/j.jinf.2008.10.003](https://doi.org/10.1016/j.jinf.2008.10.003). [PubMed: [19027169](https://pubmed.ncbi.nlm.nih.gov/19027169/)].
 84. Washburne JF, Bocchini JJ, Jamison RM. Summertime respiratory syncytial virus infection: epidemiology and clinical manifestations. *South Med J*. 1992;**85**(6):579–83. [PubMed: [1604385](https://pubmed.ncbi.nlm.nih.gov/1604385/)].
 85. Denny FW, Clyde WJ. Acute lower respiratory tract infections in non-hospitalized children. *J Pediatr*. 1986;**108**(5 Pt 1):635–46. [PubMed: [3009769](https://pubmed.ncbi.nlm.nih.gov/3009769/)].
 86. Glezen WP, Frank AL, Taber LH, Kasel JA. Parainfluenza virus type 3: seasonality and risk of infection and reinfection in young children. *J Infect Dis*. 1984;**150**(6):851–7. [PubMed: [6094674](https://pubmed.ncbi.nlm.nih.gov/6094674/)].
 87. Murphy B, Phelan PD, Jack I, Uren E. Seasonal pattern in childhood viral lower respiratory tract infections in Melbourne. *Med J Aust*. 1980;**1**(1):22–4. [PubMed: [6244480](https://pubmed.ncbi.nlm.nih.gov/6244480/)].
 88. Carballal G, Videla CM, Espinosa MA, Savy V, Uez O, Sequeira MD, et al. Multicentered study of viral acute lower respiratory infections in children from four cities of Argentina, 1993–1994. *J Med Virol*. 2001;**64**(2):167–74. [PubMed: [11360249](https://pubmed.ncbi.nlm.nih.gov/11360249/)].
 89. Downham MA, McQuillin J, Gardner PS. Diagnosis and clinical significance of parainfluenza virus infections in children. *Arch Dis Child*. 1974;**49**(1):8–15. [PubMed: [4361892](https://pubmed.ncbi.nlm.nih.gov/4361892/)].
 90. Lewis VA, Champlin R, Englund J, Couch R, Goodrich JM, Rolston K, et al. Respiratory disease due to parainfluenza virus in adult bone marrow transplant recipients. *Clin Infect Dis*. 1996;**23**(5):1033–7. [PubMed: [8922798](https://pubmed.ncbi.nlm.nih.gov/8922798/)].
 91. Henrickson KJ. Parainfluenza viruses. *Clin Microbiol Rev*. 2003;**16**(2):242–64. [PubMed: [12692097](https://pubmed.ncbi.nlm.nih.gov/12692097/)].
 92. Liu WK, Liu Q, Chen DH, Liang HX, Chen XK, Huang WB, et al. Epidemiology and clinical presentation of the four human parainfluenza virus types. *BMC Infect Dis*. 2013;**13**:28. doi: [10.1186/1471-2334-13-28](https://doi.org/10.1186/1471-2334-13-28). [PubMed: [23343342](https://pubmed.ncbi.nlm.nih.gov/23343342/)].
 93. Vainionpää R, Hyytiä T. Biology of parainfluenza viruses. *Clin Microbiol Rev*. 1994;**7**(2):265–75. [PubMed: [8055470](https://pubmed.ncbi.nlm.nih.gov/8055470/)].
 94. Reed G, Jewett PH, Thompson J, Tollefson S, Wright PF. Epidemiology and clinical impact of parainfluenza virus infections in otherwise healthy infants and young children < 5 years old. *J Infect Dis*. 1997;**175**(4):807–13. [PubMed: [9086134](https://pubmed.ncbi.nlm.nih.gov/9086134/)].
 95. Maeng SH, Yoo HS, Choi SH, Yoo KH, Kim YJ, Sung KW, et al. Impact of parainfluenza virus infection in pediatric cancer patients. *Pediatr Blood Cancer*. 2012;**59**(4):708–10. doi: [10.1002/pbc.23390](https://doi.org/10.1002/pbc.23390). [PubMed: [22095941](https://pubmed.ncbi.nlm.nih.gov/22095941/)].
 96. Srinivasan A, Wang C, Yang J, Inaba H, Shenep JL, Leung WH, et al. Parainfluenza virus infections in children with hematologic malignancies. *Pediatr Infect Dis J*. 2011;**30**(10):855–9. doi: [10.1097/INF.0b013e31821d190f](https://doi.org/10.1097/INF.0b013e31821d190f). [PubMed: [21540759](https://pubmed.ncbi.nlm.nih.gov/21540759/)].
 97. Chemaly RF, Hanmod SS, Rathod DB, Ghantaji SS, Jiang Y, Doshi A, et al. The characteristics and outcomes of parainfluenza virus infections in 200 patients with leukemia or recipients of hematopoietic stem cell transplantation. *Blood*. 2012;**119**(12):2738–45. doi: [10.1182/blood-2011-08-371112](https://doi.org/10.1182/blood-2011-08-371112). [PubMed: [22246027](https://pubmed.ncbi.nlm.nih.gov/22246027/)] quiz 2969.

Table 1. Studies Worked on Frequency and Outcomes of Viral Respiratory Infections in Cancer Patients

Authors	Date	Patients	Diagnostic Method(s)	Detected Viruses										IRTI		Pneumonia ^a		Viral ^b		
				RSV	Flu A	Flu B	HCMV	HPV	HMPV	Adeno	Picornia	Corona	No (%)	Cause	No (%)	Cause	No (%)	Cause		
Borres et al.	2007	52	-	52	-	-	-	-	-	-	-	-	-	46 (88)	RSV	27 (52)	RSV	5 (19)	Pneumonia	
Salter et al.	2004 - 2009	980	IF	60 (60)	-	-	-	-	-	-	-	-	-	31 (52)	RSV	31 (52)	RSV	ND	ND	
Mazzulli et al.	1999	45	IF Cell culture RF-PCR	6 (13)	-	-	-	-	-	-	-	-	-	ND	ND	ND	ND	4 (9)	ND	
Moreira et al.	2003	67	ND	18 (27)	-	-	-	-	-	-	-	-	-	ND	ND	ND	ND	ND	ND	
Kassis et al.	2010	6	-	6	-	-	-	-	-	-	-	-	-	2 (33)	RSV	4 (67)	RSV	2 (33)	Pneumonia	
Small et al.	2002	548	DFA/IA/Cell culture	48 (9)	-	-	-	-	-	-	-	-	-	ND	ND	25 (4.6)	RSV	3 (0.5)	Pneumonia	
Ghosh et al.	1992 - 2000	249	ELISA/IF Cell culture	9 (4)	-	-	-	-	-	-	-	-	-	ND	ND	6 (2.4)	RSV	2 (0.8)	Pneumonia	
Anaisie et al.	1997 - 1998	190	IF Cell culture	56 (29)	-	-	-	-	-	-	-	-	-	ND	ND	6 (11)	RSV	3 (5)	Pneumonia	
Roghmann et al.	2003	62	Cell culture RF-PCR	9 (15)	1	3	-	5	-	3	-	-	-	18 (29)	RSV/Flu B HPV3/Flu A picorna	3 (5); 2 (3)	ND	ND	ND	
Benites et al.	2014	104	Rapid test real-time -PCR	9 (9)	3	3	-	1	3	-	24	-	-	ND	ND	ND	ND	ND	ND	
Souza et al.		44	IF real-time -PCR	-	24	-	-	-	-	-	-	-	-	ND	ND	10 (41)	Flu A	ND	5 (21)	
Rodrigues et al.	2002	8	CFscan	-	8	-	-	-	-	-	-	-	-	ND	ND	ND	ND	5	Flu A	2
Tashar et al.	2008	25	DFA Cell culture real-time -PCR	-	20	4	-	-	-	-	-	-	-	ND	ND	16	Flu	3	Flu	ND
Pollara et al.	2013	76	Multiplex real time RF-PCR	23 (30)	-	-	-	-	-	-	-	-	-	ND	ND	3 (4)	Flu A	3 (4)	Flu A	3 (4)
Redelman-Sidi et al.	2010	394	DFA Cell culture; real-time -PCR	-	45	-	-	-	-	-	-	-	-	ND	ND	6	Flu A	ND	ND	ND
Gonzalez et al.	1999	204	IF Cell culture	-	8	-	-	2	-	3	9	-	-	ND	ND	7	Flu A	7	Flu A	4
Porter et al.	1999	118	Cell culture; IE; staining	2	5	1	1	1	-	-	-	-	-	ND	ND	6	Picornia	6	Picornia	5
														2	Adeno	3	Adeno	3	Adeno	5
														2	HPV	1	HPV	1	HPV	2
														1	HPV; HCMV	1	HPV; HCMV	1	HPV	1
														4	Flu A	4	Flu A	4	Flu A	2
														1	Flu B	1	Flu B	1	Flu B	1
														2	RSV	2	RSV	2	RSV	1
														1	HPV; HCMV	1	HPV; HCMV	1	HPV	1
Jojima et al.	2001	58	PCR	-	-	-	5	-	-	-	-	-	-	ND	ND	5 (9)	HCMV	5 (9)	HCMV	6 (10)

Chang et al.	201	7	Pathology, IF, EIA, shell vial culture	-	-	-	-	10	-	-	-	-	ND	ND	ND	ND	ND	7 (4)	HCMV	2 (2)	HCMV	
Maeng et al.	2012	1554	DFA; Rapid resp; Cell culture	-	-	-	-	74	-	-	-	-	59	HPV	15	HPV	12	HPV	5	HCMV	5	ARDS and Pulmonary Hemorrhage
Srinivasan et al.	2011	820	DFA; Cell culture; Realtime PCR	-	-	-	-	83	-	-	-	-	66	HPV	17	HPV	ND	HPV	ND	ND	ND	ND
Chemaly et al.	2012	200	-	-	-	-	-	200	-	-	-	-	140	HPV	ND	HPV	60	HPV	16	HPV	16	Pneumonia
Williams et al.	2005	128	DFA; Cell culture; RT-PCR	11	20	-	-	6	22	5	2	-	20	HMPV	9	HMPV	9	HMPV	3	HMPV	3	Pneumonia
Kamboj et al.	2008	2125	DFA; Real-time PCR	1	-	-	-	-	51	-	-	-	ND	ND	ND	ND	ND	ND	1	ND	1	RSV

^a Pneumonia and other clinical lung diseases

^b Deaths attributable to viral infection.