**SARS-CoV-2 in Children with Cancer or Following Haematopoietic Stem Cell Transplant: An Analysis of 131 Patients**

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**ABSTRACT**

**Purpose.** There are limited data on SARS-CoV-2 (COVID-19) infection in children with cancer or following hematopoietic stem cell transplant (HSCT). We describe severity and outcomes of SARS-COV-2 in these patients and identify factors associated with severe disease.

**Methods.** Multi-national, observational study of children (<19y) with cancer or HSCT and SARS-CoV-2 confirmed by polymerase chain reaction. COVID-19 was classified as asymptomatic, mild, moderate, severe, or critical (≥1 organ support). Exact polytomous regression was used to determine relationship between clinical variables and disease severity.

**Results.** One-hundred-and-thirty-one patients with COVID-19 across 10 countries were identified (median age 8y). Seventy-eight (60%) had leukemia/lymphoma, 48 (37%) solid tumour and 5 primary immunodeficiency and HSCT. Fever (71%), cough (47%) and coryza (29%) were the most frequent symptoms. The median duration of detectable virus was 16 days (range, 1-79d). Forty-nine patients (37%) were hospitalized for COVID-19 symptoms and 15 (11%) required ICU-level care. Chemotherapy was delayed/modified in 35%. COVID-19 was asymptomatic in 32% of patients, mild in 47%, moderate in 8%, severe in 4% and critical in 9%. In 124 patients (95%), a full recovery was documented and four (3%) died due to COVID-19. Any co-morbidity (odds ratio, 2.94; 95% CI, 1.81-5.21), any co-infection (1.74; 95% CI1.03-3.03) and severe baseline neutropenia (1.82; 95% CI1.13-3.09) were independently and significantly associated with increasing disease severity.

**Conclusion:** While most children with cancer had asymptomatic/mild disease, 13%had severe COVID-19 and 3% died. Co-morbidity, co-infection and neutropenia may increase the risk of severe disease. Our data may help management decisions in this vulnerable population.

**INTRODUCTION**

The global COVID-19 pandemic caused by the novel SARS-CoV-2 has posed great challenges for patients with cancer. Internationally, the haematological-oncology community mobilized rapidly with the early release of recommendations for adjustments to cancer care to ensure the safety of this vulnerable population1-3,4,5,6 While data emerged early in the pandemic about the increased risks of adverse outcomes and mortality for adult cancer and haematopoietic stem cell transplant (HSCT) patients with COVID-19, the impact of the disease in children was less clear.

Overall, children are significantly less likely to develop severe or fatal COVID-19 compared to adults.7 While the exact mechanism for this remains unknown factors proposed include those thought to be protective in children such as a stronger innate immune response leading to more effective viral clearance, a weaker adaptive immunity leading to less hyperinflammation, and pre-existing immunity due to exposure to commonly circulating coronaviruses.8 While increasing age and underlying co-morbidities, including cancer, are well documented to confer an increased risk of severe disease in adult patients, there remains a paucity of paediatric data.9-11 Further, among children with cancer the impact of underlying disease (haematological or solid tumour), treatment status (active or past) and even chemotherapy interruptions on COVID-19 severity and outcome remains unknown.

The objectives of this study were to describe the severity and outcomes of SARS-COV-2 in children with cancer or following HSCT and to identify factors associated with severe disease.

**METHODS**

This was a multi-national, observational cohort study of children and adolescents (<19 years) with a diagnosis of cancer or following HSCT who had confirmed SARS-CoV-2 infection by polymerase chain reaction (PCR). Patients were included if they had a diagnosis of cancer, irrespective of treatment status, or had a HSCT for malignant or non-malignant diagnoses. For details of testing criteria of participating centers and COVID-19 country incidence see Appendix 1. The study protocol and database was developed and approved in March 2020 by the Umbrella research group, an international collaboration of paediatric oncology and infectious diseases clinicians.

De-identified data were collected retrospectively by study site investigators and entered into REDCap. COVID-19 severity was classified as (i) asymptomatic; (ii) mild (upper respiratory or gastro-intestinal symptoms) (iii) moderate (acute lower respiratory tract infection but no hypoxemia) (iv) severe (hypoxia < 92% without supplemental oxygen) or (v) critical (admission to intensive care unit (ICU), or equivalent, for organ support).12 Eligible patients were identified from microbiological reports, existing surveillance and notification systems and hospital records. Patients were followed up for a minimum of 30 days following infection diagnosis.

Active treatment was defined as any chemotherapy or radiotherapy within 30 days prior to SARS-CoV-2 infection or HSCT within 6 months prior to SARS-CoV-2 diagnosis. Intensive treatment was defined as chemotherapy more intensive than maintenance chemotherapy for acute lymphoblastic leukaemia (ALL).13 Neutropenia was defined as absolute neutrophil count (ANC) <500cells/mm3 and lymphopenia as absolute lymphocyte count (ALC) <1000cells/mm3. Overweight was defined as body mass index (BMI) >95th percentile.14

Human research and ethics approval for the multisite study was obtained at Royal Children’s Hospital, Melbourne, and site-specific ethics at participating centers as required. The study was conducted in accordance with the Declaration of Helsinki and informed consent was obtained if requested by the local ethical committee.

***Statistics***

Associations of clinical factors with the severity of disease were analyzed using univariate and multivariate exact polytomous regression, based on adjacent categories modelling.15 Exact logistic regression was used to account for the smaller sample size.16 Factors significantly associated in univariate analysis were used for stepwise forward multivariate analysis using LogXact 10 software from Cytel Software Corporation (Cambridge, MA, U.S.A.). Two-sided tests were used throughout and *P*-values <0.05 were considered significant.

**RESULTS**

Twenty tertiary paediatric hospitals across 10 countries contributed data to the study from beginning of pandemic until end of February 2021 applying different testing strategies (Appendix 1). Of the 146 patient episodes entered, 15 were excluded from this analysis (8 with non-cancer or HSCT-related immunosuppression, 5 with COVID-19 diagnosed on serology only and 2 with COVID-19 prior to cancer diagnosis) (Figure 1). Of the remaining 131 episodes, 108 were on active treatment (including 8 with HSCT within 6 months before SARS-CoV-2 diagnosis), and 23 had completed treatment (including 6 with HSCT >6 months before SARS-CoV-2 diagnosis) (Figure 1). See Table 1 for demographic information. For the 23 patients that had completed cancer treatment, the median time from their last dose of chemotherapy to infection was 1.5 years (range, 0.2-7.4 years).

Disease severity was categorized as asymptomatic in 42 patients (32%, 95% CI, 24%-41%), mild in 61 (47%, 95% CI 38%-55%), moderate in 11 (8%, 95% CI 4%-14%), severe in 5 (4%, 95% CI 2%-8%) and critical in 12 (9%, 95% CI 5%-15%).

***Acquisition, incubation and shedding***

Virus acquisition was known in 93 episodes, and included 79 (85%) with community-acquired and 14 (15%) with hospital-acquired infection. Fifty-eight (44%) infections were part of a SARS-CoV-2 family cluster. The median duration from known SARS-CoV-2 exposure to earliest onset of symptoms or positive PCR result for asymptomatic cases was 5 days (range, 1-22 days) in the 26 episodes where the date of exposure was known. In 42 asymptomatic patients, testing indication included confirmed contact (n=14), pre-general anaesthetic (n=8), pre-chemotherapy (n=8) and pre-HSCT (n=6) (unknown, n=6).

The median duration of virus detection by PCR was 16 days (IQR, 9.5-27 days; range, 1-79 days) in the 51 patients (including 48 on active treatment) with 2 or more positive respiratory swabs.

***Symptoms and signs***

There was no difference in the proportion of patients with symptomatic infection who were on active cancer treatment (69%) or who had completed treatment (65%). In the 89 symptomatic patients, fever (≥38°C) was the most common symptom (Table 2). Chest computerized tomography (CT) was performed in 27 patients, with bilateral ground glass changes in 14 and bilateral consolidation in 6 (normal in 7). A co-infection was diagnosed at the time of diagnosis (± five days) of SARS-CoV-2 in 16 patients (12%), with bacterial co-infection the most common (n=7) (Table 1).

***Management***

Sixty-five (50%) patients were admitted to hospital at the time of infection, including 49 (37%) for COVID-19 related symptoms or management and 16 (12%) for chemotherapy or other non-COVID-19 related treatment. Of the 49 patients admitted due to COVID-19, the median hospital length of stay (LOS) was 9.3 days (IQR, 4.5-19.6 days). Of the 100 patients on active cancer treatment, 36 (36%) had chemotherapy interrupted or dose-modified (Table 2). On univariate analysis, any chemotherapy modification (interrupted or dose-modified) was not significantly associated with a reduced risk of severe COVID-19 (OR 0.72, 95% CI 0.46-1.05) in all patients or in the 31 patients on intensive chemotherapy (OR 0.62, 95% CI 0.20-1.39).

Specific treatments are documented in Table 2. Antiviral or other potentially COVID-19 directly therapy was used infrequently (8%). Children with severe or critical disease were more likely to receive antiviral therapy (47% versus 3%) or corticosteroids (52% versus 2%) compared to those with non-severe disease. Forty-three (32%) patients had broad-spectrum antibiotics (>1 agent in 32), most commonly an anti-pseudomonal beta-lactam or cephalosporin (n=33).

Fifteen patients (11%, 95% CI, 7% to 18%) required ICU admission, including 10 who required mechanical ventilation (median duration 7.5 days, IQR 3.8-11.8 days). The patients requiring ICU admission were treated for leukemia/lymphoma (n=10) and solid tumour (n=5) in Brazil (n=10), Russia (n=2), Germany (n=2) and Israel (n=1), with a median age of 7 years (range, 5-16y). No SARS-CoV-2 variant was found in these patients. One patient had a co-infection with *S. aureus/E. coli* and cytomegalovirus, another patient a co-infection with *Pneumocystis jirovecii.* The median ICU LOS was 10 days, IQR 6-19 days, with 14 patients requiring prolonged (>3d) admission.

***Blood biomarkers***

Full blood examination was available in 109 patients of which 72 (66%) were lymphopenic and 24 (22%) were neutropenic at SARS-CoV-2 diagnosis. C-reactive protein was available in 59 (45%) patients with the median peak value significantly higher in those with severe/critical disease compared to non-severe/critical disease (126 [IQR, 66-287] versus 21 [4.6-57], *P*<0.001).

***Outcome***

A total of 124 (95%) patients made a full recovery. Myocarditis was documented in two patients and encephalitis in one, all of whom recovered fully (all on active treatment). One patient, also on active treatment, had a protracted course and developed post-infectious bronchiolitis obliterans. Five patients died within 30 days, including 4 (3%; 95% CI, 1% to 7%) due to COVID-19 infection (Table 3). These four patients died between 6 and 21 days after diagnosis of the infection. Of the four COVID-19 related deaths, one was on active treatment (1% of 108 patients on active treatment) and three had completed cancer treatment (13% of 23 with completed treatment). Final outcome unknown in 2 patients.

Factors significantly associated with increasing disease severity in univariate analysis included presence of any co-morbidity, chronic lung disease, any co-infection, bacterial co-infection and neutropenia. On multivariate analysis, co-morbidity, bacterial co-infection and neutropenia remained independently and significantly associated with increasing disease severity (Table 4).

**DISCUSSION**

In the multi-national study of children with cancer or HSCT, infection with SARS-CoV2 was asymptomatic in almost one third of children, with fever, cough and coryza as the most common symptoms in the remaining patients. Although 95% of patients made a full recovery, severe or critical disease occured in 13%, and 11% required prolonged ICU admission. Factors significantly associated with increasing COVID-19 severity included presence of at least one co-morbidity, bacterial co-infection and neutropenia. Overall mortality was 3% and higher in patients who had completed cancer treatment or had undergone HSCT (13%) compared to patients on active treatment (0.9%). For patients on active treatment, chemotherapy was modified/interrupted in 35% and while no significant association of any adjustment with disease severity was seen for all patients on active treatment, the wide confidence intervals limit firm conclusions.

Since SARS-CoV-2 was first reported, marked variation in the incidence of severe or critical disease in children with cancer has been described, ranging from 0 through to 15%.17-20 Similarly, variation in infection-related mortality has also been described, with many large paediatric cancer centers reporting no deaths,18,20,21 while others, albeit small single-center studies, reporting case fatality up to 28%.22 This variation likely reflects the different populations included (e.g., hospitalized versus non-hospitalized), available resources to manage patients and COVID-19 testing criteria. The overall mortality of 3% in our study is in keeping with results of a systematic review of five small studies of COVID-19 in paediatric cancer (pooled mortality of 4%),23 as well as the St Jude Global registry of COVID-19 (3.7%)(<https://global.stjude.org/>). Mortality was higher in patients that had completed cancer treatment, as compared to those on active treatment, although the small number limits firm conclusions. This observation is in contrast to adult patients, where patients on systemic anticancer therapy had a similar risk of death to patients on no treatment.23 Factors such as increasing age, co-morbidities and potentially a protective effect of corticosteroids in children on active treatment are some hypotheses that may explain these results.8

Children with cancer are a heterogeneous population, with a spectrum of infection risk that varies both between cancer diagnoses and during the course of treatment.24 While paediatric cancer has not consistently been identified as a risk for severe or fatal COVID-19, most studies have grouped solid tumour, leukemia, relapsed disease and HSCT together.23 An understanding of the impact of these disease- and treatment-related factors is critical to informing paediatric cancer-care pathways including modifying chemotherapy regimens and isolation restrictions. Although chemotherapy intensity, relapse-status, active treatment and baseline lymphopenia were not significantly associated with disease severity in our cohort, neutropenia at time of infection with SARS-CoV-2 increased the odds of severe disease. Similar to adult literature, the presence of a co-morbidity also increased odds of severe disease.25 Not surprisingly, in our cohort, an increased odds of severe disease was observed in patients with co-infection at the time of SARS-CoV-2 diagnosis. To date, this association has not been well described in the paediatric oncology literature. Notably, the emerging reports of invasive mould co-infections, including aspergillosis26,27 and mucomycoses,28 was not reflected in our data with only three IFIs documented, one of which was with *Aspergillus* spp.

Duration of viral shedding in the cancer population has important infection-control implications given the necessity for frequent hospital attendance and potential for nosocomial transmission. A study in otherwise well children found the median period of viral shedding of COVID-19 was 15 days (IQR 11-20d) and shorter in asymptomatic patients (11 vs 17d).29 Similarly, the median duration of SARS-CoV-2 detected by PCR was 16 days in our study, although in one patient, virus was detected by PCR for 79 days. While a theoretical risk of transmission remains, there are limited data on viability of the virus in patients with prolonged shedding or the potential to reactive and cause severe disease in subsequent chemotherapy cycles.

In our study, most known acquisitions occurred within the family home. In addition to the vaccination of treating physicians and nurses, vaccination of household contacts against COVID-19 may be another important protective measure. As adult cancer patients have an increased risk of severe disease and death, vaccination of this patient population is now a priority for many centres. While an immune correlate of protection against COVID-19 has not been established to date, a study of adult cancer patient on active treatment found 90% exhibited antibody response to an mRNA vaccine, albeit significantly lower than in healthy controls.30. Although vaccination of children has commenced in some regions, there are no data on vaccine efficacy in the paediatric cancer population, and clinical studies are urgently needed.

Highly effective antiviral or adjunctive treatment of COVID-19 in children continues to remain elusive. While relatively few patients received targeted treatment in our cohort, patients with more severe disease were more likely receive one or more antiviral or adjuvant treatments. The range of agents used also reflects the evolving evidence during the pandemic and includes medications such as hydroxychloroquine, ribavirin, remdesivir and azithromycin that are no longer recommended in this setting.31

 Notably, over one third of patients on active treatment had chemotherapy interruptions due to COVID-19, including cycles withheld in 30%, which, may impact treatment response and risk of relapse. Corroborating our data, a study in 308 adult cancer patients demonstrated that continuing cytotoxic chemotherapy administration was not significantly associated with a severe or critical COVID-19 event25.

Although one of the largest cohorts of COVID-19 in paediatric patients with cancer published to date, our data are retrospective and variations in testing criteria between centers may impact the spectrum of disease severity reported. As only PCR-confirmed infections were included, this may have also led to an over estimation of disease severity. Included patients may have been entered into other international or country-based registries which has important implications for interpreting data from meta-analyses. Finally, as data collection ended in February 2021, the impact of newer variants including Delta-variant on disease severity remains unknown.

Our study provides new insights into factors associated with COVID-19 disease severity, duration of shedding, symptoms and outcomes in children with cancer, which could be helpful in the clinical management of this patient population. Although almost all children made a full recovery, severe or critical disease still occurred in 15% of patients and 3% died. A high awareness for increased COVID-19 severity is recommended in children with cancer and co-morbidities, baseline co-infection or severe neutropenia. Ongoing surveillance is critical to monitor vaccine efficacy and impact of emerging COVID-19 variants in this population.

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**LEGENDS**

**Table 1.** Demographic data of children with cancer or following hematopoietic stem cell transplantation and SARS-CoV-2 infection confirmed by PCR

\*Unknown in n=43

\*\*Includes children with brain tumour affecting the pituitary stalk (n=4) or long term immunosuppression (n=3)

\*\*\*All patients in whom the tumour has caused brain damage

\*\*\*\* Includes patients with Down syndrome, psoriasis, xeroderma pigmentosum, Niemann-Pick disease, kidney transplantation, Kaposi sarcoma, Russel´s syndrome

IQR interquartile range; GVHD graft-versus-host disease; BMI body mass index

**Table 2.** Symptoms, treatment and outcomes of children with cancer or following hematopoietic stem cell transplantation and SARS-CoV-2 infection confirmed by PCR

ICU intensive care unit; ECMO extra-corporeal membrane oxygenation

**Table 3:** Clinical details of children with cancer and lethal outcome due to SARS-CoV-2 infection

HSCT hematopoietic stem cell transplantation; ANC absolute neutrophil count; ALC absolute lymphocyte count; ARDS acute respiratory distress syndrome

**Table 4.** Associations of patient characteristics with disease severity based on results of exact polytomous regression

HSCT hematopoietic stem cell transplantation; OR odds ratio; CI confidence interval; vs versus; NS non significant

**Figure 1:** Consort diagram on patients included in the registry and analyzed

HSCT hematopoietic stem cell transplantation

|  |  |
| --- | --- |
|  | N=131 |
| Median age, (IQR) | 8 (4-14) |
| Male sex, n (%) | 75 (57) |
| Country, n (%)-Austria-Germany-Italy-Switzerland-UK-Brazil-Canada-Russia-Israel-Australia | 10 (8)26 (20)5 (4)2 (1.5)2 (1.5)41 (31)21 (16)12 (9)9 (7)3 (2) |
| Underlying diagnosis, n (%)-Leukemia-Lymphoma-Solid tumour-HSCT for primary immunodeficiency  | 60 (46)18 (14)48 (37) 5 (4) |
| Active cancer treatment, n (%)-Intensive chemotherapy, n | 100 (76)31\* |
| GVHD, n (%)-Acute (Grade 1, n=1; Grade 2, n=1)-Chronic-Unknown | 2 (2)2 (2)1 (0.8) |
| CAR-T treatment, n (%) | 3 (2) |
| No co-morbidity, n (%)At least 1 co-morbidity-Overweight (BMI >95th percentile)-Panhypopituitarism or adrenal insufficiency\*\*-Chronic neurological disease\*\*\*-Chronic lung disease (other than asthma)-Hypertension-Diabetes (including steroid-induced)-Asthma-Hypogammaglobulinemia-Other chronic disease\*\*\*\* | 96 (73)35 (27)875442227 |
| Bacterial co-infection (n=5)-Blood stream infection-*E coli* urinary tract infection-*S. aureus* soft tissue infection-*Mycobacterium tuberculosis* peritonitis | 4111 |
| Viral co-infection (n=5)-Cytomegalovirus (blood)-Enterovirus/rotavirus enteritis-Parainfluenza respiratory tract infection-Herpes simplex virus gingivostomatitis | 2111 |
| Invasive fungal infection (n=3)-Disseminated aspergillosis, *-Pneumocystis jirovecii* pneumonia *-Candida tropicalis* urinary tract infection | 111 |
| Median neutrophil count (cells/mm3) |  |
| Median lymphocyte count (cells/ mm3) |  |

**Table 1**

|  |  |
| --- | --- |
|  | N |
| **COVID-19 symptoms (n=89)** |
| -Fever ≥38°C-Cough-Coryza-Any gastrointestinal symptom -Dyspnoea-Sore throat-Anosmia or loss of taste-Myalgia/arthralgia-Rash  | 6342 26 21 17 10 6 6 4  |
| **COVID-19 treatment** |
| Any antiviral therapy (n=11)OseltamivirHydroxychloroquineRibavirinLopinavir/ritonavirRemdesivir | 63111 |
| Azithromycin | 17 |
| Any adjunctive therapy (n=13) CorticosteroidsImmunoglobulinTocilizumabConvalescent plasmaAnticoagulation | 118531 |
| Supplemental O2 | 17 |
| **Chemotherapy changes** |
| WithheldModifiedUnknownNo change | 306163 |
| **Outcome** |
| ICU admission-Mechanical ventilation-Inotropic support-ECMO | 15 10 10 0 |
| Disease severity-Asymptomatic-Mild-Moderate-Severe-Critical | 42 61 11 5 12  |
| Died-COVID-19 related-Disease progression | 5 4 1  |

**Table 2**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Age (y)/sex | Country | Malignancy | Last anti-cancer treatment | Co-morbidity | ANC/ALC at diagnosis of SARS-CoV-2 (per mm3) | Co-infection | Mechanical ventilation | Antiviral Treatment | Time between SARS-CoV-2 diagnosis and death (days) |
| 6/female | Russia | Acute leukemia | HSCT>6 months | Kaposi sarcoma | 3900/780 | No | Yes (ARDS) | Ribavirin, lopinavir, hydroxychloroquine | 18 |
| 9/female | Brazil | Acute leukemia | 5 days before | Steroid induced adrenal insufficiency | 0/0 | No | Yes (ARDS) | No | 21 |
| 11/female | Brazil | Brain tumor | >30 days before | Steroid induced adrenal insufficiency, obsesity | 3680/3320 | No | Yes (ARDS) | Oseltamivir | 9 |
| 11/female | Brazil | Brain tumor | >30 days before | Steroid induced adrenal insufficiency, obesity, chronic neurological problems | 7080/2730 | No | Yes (ARDS) | No | 6 |

**Table 3**

|  |  |  |
| --- | --- | --- |
|  | **Univariate** | **Multivariate** |
|  | **OR (95% CI)** | **P value** | **OR (95% CI)** | **P value** |
| Europe vs Non-Europe | 1.31 (0.93-1.92) | 0.13 | - | - |
| Age ≤7 years vs >7 | 1.28 (0.93-1.81) | 0.13 | - | - |
| Male vs female | 0.88 (0.65-1.20) | 0.45 | - | - |
| Leukemia v solid tumour | 1.35 (0.99-1.87)  | 0.06 | - | - |
| Intensive vs non-intensive treatment phase | 1.24 (0.88-1.73) | 0.23 | - | - |
| Radiotherapy vs no radiotherapy | 1.19 (0.83-1.67) | 0.35 | - | - |
| Relapse/progressive vs non-relapse/progressive malignancy  | 1.17 (0.77-1.74) | 0.49 | - | - |
| HSCT vs no HSCT | 1.22 (0.80-1.79) | 0.36 | - | - |
| CAR-T vs non CAR-T | 0.63 (0.06-2.11) | 0.82 | - | - |
| Active vs no active cancer treatment at SARS-CoV-2 diagnosis | 1.09 (0.73-1.59) | 0.70 | - | - |
| Any co-morbidity vs no co-morbidity | 1.90 (1.35-2.74) | <0.001 | 2.94 (1.81-5.21) | <0.001 |
| Chronic lung disease vs no | 2.68 (1.25-7.09)  | 0.010 | NS | NS |
| Co-infection vs no co-infection at SARS-CoV-2 diagnosis | 1.44 (1.00-2.06) | 0.047 | 1.74 (1.03-3.03) | 0.036 |
| Bacterial co-infection vs no at SARS-CoV-2 diagnosis | 1.71 (1.05-2.76) | 0.032 | NS | NS |
| Neutropenia vs no neutropenia at SARS-CoV-2 diagnosis | 1.54 (1.07-2.25)  | 0.021 | 1.82 (1.13-3.09) | 0.013 |
| Lymphopenia vs no lymphopenia at SARS-CoV-2 diagnosis | 1.19 (0.83-1.77) | 0.39 | NS | NS |

**Table 4**



**Figure 1**