Dear Editor

Thank you for sharing your reviewers' comments. We have given answers to each of them. In accordance with the reviewers' suggestions, we also revised our manuscript.

Dear Reviewer,

Thank you for your comments. We hope you will find our responses satisfactory. If any other explanation is needed, we will be happy to follow the instructions.

The potential reasons explaining early diagnosis of CVID in some countries should be briefly analysed (i.e. in Germany). The same for differences in diagnostic delay.

We agree that such an assessment would add much value to this review. Unfortunately, it is very difficult to compare data from different countries. We recently published in 2020 a detailed analysis of the diagnostic delay in Poland in comparison to other countries (ref 6) and we did want to repeat data, however following your suggestion a paragraph and references were added:

At present, in Poland, CVID diagnosis is more rapid than that before 2000 [6]. However, there remains a low percentage of patients whose diagnosis was established within a year of occurrence of the first symptoms [6]. According to the 2014 ESID registry, a significant shortening of the median delay was achieved only in Spain (9.0 vs. 4.6 years) [2]. There is a need for further research on the relationship between delayed diagnosis and occurrence of complications. It is difficult to compare data coming from different countries and studies, due to different methodology applied for analysis. In our experience, a significant increase in the number of diagnosed CVID cases occurred when reimbursement of subcutaneous immunoglobulin treatment for adult patients with primary immunodeficiency was provided and specialized immunology centers established [6,14].

Please further information about common viral infections (i.e. influenza) or emerging infection (i.e. COVID-19) in CVID.

Thank you for bringing this important issue to our attention. New data and references were added.

In contrast to high risk of common bacterial infections patients with CVID do not present an increased susceptibility for influenza. Moreover most them have preserved antigen specific T

cell responses after influenza vaccination [20]. Data about the clinical course of Coronavirus disease 2019 (COVID-19) in patients with primary immunodeficiency remains limited. The first, published case series included 5 patients with CVID and 2 patients with agammaglabulinemia [21]. Patients with CVID presented with a severe form of COVID-19 infection. They required multiple drug treatment, including antiretroviral agents, IL-6 blocking drugs, and mechanical ventilation. In contrast 2 patients with agammaglobulinemia and absent B cells, had mild symptoms. Authors speculate that strikingly different clinical course of COVID 19 might be explained by a possible role of B lymphocytes in the SARS-CoV-2 induced inflammation, assuming that patients with agammaglobulinemia lack B lymphocytes whereas patients with CVID have dysfunctional B lymphocytes [21].

A suggestion on the Interval to perform diagnostic imagen and pathology biopsy to early diagnose of cancer (i.e. gstric) is wellcome.

Thank you for suggestion. We discussed this topic as follow:

As CVID patients also have an increased risk of gastrointestinal lymphoma, it seems reasonable to perform multiple biopsies from the gastric antrum and body and additionally from the second part of the duodenum. It is reported that fewer biopsies decreased the probability of detecting early premalignant lesions [51]. Dhalla et al. suggested to perform upper endoscopy with an interval between the subsequent endoscopic assessments based on histological findings: every 1–3 years in CVID patients with metaplasia, every 3 years in patients with atrophic gastritis, and every 6–12 months in those with dysplasia [52]. However, some CVID patients developed a high-grade gastric cancer 12–14 months after an endoscopy that had shown no histologic signs of dysplasia. Based on this data a yearly evaluation for gastric cancer in all CVID patients might be beneficial [50,53]. Development of further guideline/consensus on screening and monitoring for gastric cancer and lymphomas is required.

Please suggest what is considered a low specific antibody response for diagnose of CVID.

Thank you for comment. The definition was added.

The vaccination response in adults is satisfactory if at least 70% of the measured serotype-specific antibodiy titers are above 1.3 µg/ ml or a four-fold increase of the pre-vaccination titers for more than 17 of 23 serotypes is observed at week 4 after immunization [59].

The potential role of T-cell activation phenotype should be discussed.

Thank you for suggestion. Paragraph was rewritten and new references were introduced.

T cells play a central role in B cell activation and differentiation into memory and IgG producing B cells. Various reports have associated CVID with other findings, such as CD4 T-cell lymphopenia with reduced counts of naive CD4 T cells [66] and naive CD8mT-cell [67]. Regulatory T cells (Treg), Th17, and follicular T helper (Tfh17) cells were specifically reduced in patients with complicated CVID phenotypes [68]. T cells in CVID have lower proliferative capacities. [Azizi G] [69] and abnormal cytokine production.[70]. Low (naïve) CD4 T cells are associated with complications and a poor prognosis in CVID [71]. Recent publications show an involvement of follicular T cells in CVID pathogenesis [72]. An increase of circulating memory $CXCR5^{+}$ CD4 T cells in CVID patients with non-infectious complications has been reported [73]. The cells could participate in autoimmune manifestations through their role as B cell inducers. As a consequence patients with CVID and autoimmune phenomena exhibit hyperplastic, however insufficient, germinal center (GC) response. An enrichment of T cells in lymph nodes of patients with CVID with lymphadenopathy and preserved ability to form GCs has been found.[74]. Taken together, these data suggest that some distinct pathophysiological alterations are present in a defined subgroup of CVID patients. Work has also been done to better understand correlations between B cell and T cell abnormalities with unique clinical profiles and to use them as a prognostic marker [68,75].