Unmet Challenges in COVID-19 Prevention for Immunocompromised Individuals: A Consensus Analysis from Portugal

Desafios Não Atendidos na Prevenção da COVID-19 em Indivíduos Imunocomprometidos: Uma Análise de Consenso em Portugal

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ABSTRACT

Introduction: The COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), resulted in significant disease burden and mortality. Despite vaccination successes, new virus variants persist, affecting unvaccinated and immunocompromised individuals (ICI) severely. These high-risk groups face elevated mortality and hospitalization rates. Vigilance and targeted health measures remain crucial post-pandemic. The aim of this study was to develop consensus on the unmet needs in COVID-19 prevention among ICI.
Methods: We performed a Delphi study involving 45 experts, including physicians, health managers, policymakers, public health experts, members of medical societies and patient organizations. Consensus was achieved at 65% for each identified strategy using a scale ranging from "strongly agree" to "strongly disagree." Three Delphi rounds were conducted to address four key questions: identifying unmet needs in COVID-19 prevention for ICI; identifying the characteristics that distinguish ICI as a susceptible group; determining the main outcomes of COVID-19 in ICI; and indicating action plans for protecting ICI. The first round involved voting on pre-identified indicators. The second and third rounds involved analyzing the gathered information and voting on each indicator to achieve consensus.
Results: A retention rate of 80% was achieved. Out of 89 valid indicators analyzed, 23 achieved consensus. These included: eight indicators highlighting the importance of raising awareness about COVID-19 and vaccination outcomes, ensuring safety and understanding, and developing targeted immunization strategies for ICI; five indicators identifying susceptible groups within ICI, such as individuals undergoing chemotherapy or radiotherapy, those with primary immunodeficiencies, solid organ transplant recipients, patients with chronic kidney disease, and bone marrow transplant recipients; two indicators showing improvements in clinical outcomes and reduced hospitalizations; and eight indicators recommending the development of effective therapies, more immunogenic vaccines, and treatments for viral infections in ICI.
Conclusion: The study emphasized the importance of targeted immunization strategies, monitoring, and tailored education to address diverse needs of ICI. These findings provide a foundation for future policies to effectively manage and protect ICI during and beyond the COVID-19 pandemic.
Keywords: COVID-19/prevention and control; Delphi Technique; Immunocompromised Host; Portugal; SARS-CoV-2

RESUMO

Introdução: A pandemia de COVID-19, causada pelo coronavírus da síndrome respiratória aguda grave 2 (SARS-CoV-2), resultou numa carga significativa de doenças e mortalidade. Apesar dos sucessos das vacinas, novas variantes do vírus persistem, afetando gravemente indivíduos não vacinados e imunocomprometidos (IIC). Estes grupos de alto risco enfrentam taxas elevadas de mortalidade e hospitalização. A vigilância e as medidas de saúde direcionadas permanecem cruciais após a pandemia. Este estudo teve como objetivo desenvolver um consenso sobre as necessidades não atendidas na prevenção da COVID-19 entre IIC.
Métodos: Realizámos um Delphi envolvendo 45 especialistas, incluindo médicos, gestores de saúde, decisores políticos, especialistas em saúde pública, membros de sociedades médicas e organizações de doentes. O consenso foi alcançado em 65% para cada estratégia identificada, utilizando uma escala que varia de "concordo totalmente" a "discordo totalmente". Foram realizadas três rondas Delphi para abordar quatro questões principais: identificar necessidades não atendidas na prevenção da COVID-19 para IIC; identificar as características que distinguem os IIC como um grupo suscetível; determinar os principais resultados da COVID-19 em IIC; e indicar planos de ação para proteger os IIC. A primeira ronda envolveu a votação de indicadores pré-identificados. As segunda e terceira rondas envolveram a análise das informações recolhidas e a votação de cada indicador para alcançar consenso.
Resultados: Foi alcançada uma taxa de retenção de 80%. Dos 89 indicadores válidos analisados, 23 alcançaram consenso. Estes incluíram: oito indicadores que destacaram a importância de aumentar a consciencialização sobre a COVID-19 e os resultados da vacinação, garantindo segurança e compreensão, e desenvolvendo estratégias de vacinação direcionadas para IIC; cinco indicadores que identificaram grupos suscetíveis dentro dos IIC, como indivíduos em quimioterapia ou radioterapia, aqueles com imunodeficiências primárias, recetores de transplantes de órgãos sólidos, pacientes com doença renal crónica e recetores de transplantes de medula óssea; dois indicadores que mostraram melhorias nos resultados clínicos e redução das hospitalizações; e oito indicadores que recomendaram o desenvolvimento de terapias eficazes, vacinas mais imunogénicas e tratamentos para infeções virais em IIC.
Conclusão: O estudo enfatizou a importância de estratégias de vacinação direcionadas, monitorização e educação personalizada para abordar as diversas necessidades dos IIC. Estes resultados fornecem uma base para o desenvolvimento de políticas futuras que visem gerir e proteger eficazmente os IIC durante e após a pandemia de COVID-19.
Palavras-chave: COVID-19/prevenção e controlo; Hospedeiro Imunocomprometido; Portugal; SARS-CoV-2; Técnica Delphi

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INTRODUCTION

The COVID-19 pandemic, resulting from the rapid global spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was responsible, until July 7th, 2024, for approximately 775 673 955 cases of COVID-19 and 7 053 524 associated deaths worldwide.[1] During the same period, Portugal reported 5 657 579 cases and 28 556 associated deaths.[1]

The COVID-19 pandemic has had a profound impact on multiple sectors of society, disrupting healthcare, education, and the global economy.[2] The high morbidity and mortality rates overwhelmed healthcare systems, reduced workforce productivity, and triggered economic recessions due to lockdown measures aimed at controlling the virus's spread.[2,3] To meet the increasing demand for hospitalizations and intensive care, particularly for severe cases,[4] significant health resources were mobilized.[2] In response to this extraordinary challenge, unprecedented measures were implemented, primarily focusing on healthcare. Governments expanded ICU capacities, redeployed healthcare professionals, and allocated emergency resources to procure ventilators, personal protective equipment (PPE), and strengthen hospital infrastructure.[3,5] The effectiveness of vaccination has significantly transformed the course of the pandemic, reducing morbidity, mortality,[3,6-8] and the case-to-death ratio.[3] The success of vaccination efforts over the last almost four years reflects the positive impact of medical interventions in combating COVID-19.[1] Globally, as of December 31st, 2023, a total of 5.47 billion COVID-19 vaccine doses had been administered, including 9 822 021 in Portugal.[1]

However, despite these achievements, SARS-CoV-2 continues to infect individuals and cause severe illness and death.[9] Although the World Health Organization (WHO) has officially declared the end of the pandemic in May 2023, it has warned of the persistence of the virus, its transmission, and the risk of new mutations with the potential to escape vaccine protection and cause new waves of infections and deaths.[8] The WHO also emphasized that the official end of the pandemic period should not mean reducing vigilance in existing alert and response systems or minimizing the importance of precautions against COVID-19.[8]

Portugal still faces the repercussions of COVID-19.[1] According to data released by the Directorate-General of Health (DGS) in Portugal on July 24th, 2024, the virus continues to claim a considerable number of lives, with 787 deaths reported since January 1st, 2024.[10]

Among the populations with the highest risk of suffering more profound consequences of the infection are unvaccinated and immunocompromised individuals (ICI).[9,11,12] Unvaccinated individuals miss the immunological protection offered by vaccines, which typically guards against infection and its severe effects.[12] Moreover, they pose a challenge to public health efforts, being major contributors to viral transmission and evolution.[13] The widespread transmission of the virus creates opportunities for favorable mutations to emerge via natural selection.[14] This heightened risk presents a particular challenge for vulnerable populations, who face greater susceptibility to severe infection and increased mortality rates.[14]

In parallel, certain individuals with diverse immunocompromising health conditions or specific conditions experience varying levels of immunosuppression – persons with hematologic or solid organ cancers, hematopoietic stem cell or solid organ transplants, primary immunodeficiency disorders, advanced or untreated human immunodeficiency virus (HIV) infection, and those on chronic use of immunosuppressive medications, hindering their ability to generate an immune response to the COVID-19 vaccination.[15] Consequently, they may face heightened vulnerability to COVID-19, despite being fully vaccinated, increasing the risk of severe infections necessitating hospitalization and prolonged virus transmission.[15]

Within the diverse spectrum of ICI, various groups face heightened risks of severe COVID-19 outcomes. These include individuals with primary or secondary immunodeficiencies, such as cancer patients, especially those with hematologic neoplasms, transplant recipients, those on immunosuppressive medication, individuals with autoimmune diseases, those living with HIV/ acquired immunodeficiency syndrome (AIDS), and those with chronic kidney disease.[3,9,14] Immunocompromised

individuals are more likely to require Intensive Care Unit (ICU) hospitalization and experience in-hospital mortality, irrespective of vaccination status.[9] Intensive Care Unit data offers critical insights into the severe consequences of COVID-19, including individuals spanning the immune spectrum and facilitating more conclusive findings.[16] Notably, data from the United States in 2022 indicate that over 12% of hospitalized COVID-19 patients were immunocompromised, underscoring their heightened vulnerability.[9]

Despite the relevance of this evidence, there are still significant gaps in the literature regarding the unmet needs of ICI in the context of COVID-19 prevention. In this study we aimed to contribute to filling this gap by developing a consensus on the main vulnerabilities of ICI, understanding the main outcomes of COVID-19 in this population, and designing actionable strategies to safeguard their health.

METHODS
Study design
To achieve the objectives of this study, we selected the Delphi technique, which is a consensus-building methodology that aims to reach consensus on a complex subject by a systematic forecasting process that draws on the combined knowledge of a group of specialists.[17,18] The technique involved the participation of specialists in the field of study, therefore guaranteeing informed insight and credibility.[18,19] This study convened a multidisciplinary panel of experts, encompassing physicians from different specialties (Infectious Diseases, Neurology, Immuno-Allergology, Nephrology, Internal Medicine, Rheumatology, Pulmonology and Hematology), as well as health managers, policy makers and consultants, public health specialists, members of medical societies and members of patient associations. These experts were selected through purposive sampling to ensure a comprehensive representation of perspectives and expertise relevant to the study, particularly from medical specialties with a fundamental role in this area, and ensuring a balanced representation across stakeholder groups, including considerations for geographic distribution. Participants were informed about the study methodology and objectives before providing informed consent for participation.

The questions formulated to perform the Delphi panel were informed primarily by literature review and experts' consultation.

The Delphi process comprised three successive rounds of data collection.[17,20] To begin the first round, the experts were asked four question, aimed at: 1) identifying unmet needs in COVID-19 prevention in ICI, based on their perceptions and clinical experience, inform and develop effective prevention measures for this population; 2) identifying the characteristics that distinguish ICI as a susceptible group in terms of COVID-19; 3) determining the main outcomes

of COVID-19 in ICI; 4) developing the most effective action plans for protecting ICI in a COVID-19 prevention context.

Participants rated the following questions (Q) on a Likert scale ranging from "strongly agree", "agree", "neither agree nor disagree", "disagree", to "strongly disagree":

- Q1 –"In your perception, based on your clinical practice, management experience or contact with associates, what needs remain to be met in the prevention of COVID-19 in immunocompromised individuals (ICI)?"
- Q2 – "Who do you consider to be immunocompromised individuals (ICI), i.e. which ICI characteristics are related to COVID-19 susceptibility?"
- Q3 – "Currently, in your perception, what do you consider to be the main outcomes of COVID-19 in immunocompromised individuals (ICI)?"
- Q4 – "Regarding the need to prevent COVID-19 in immunocompromised individuals (ICI), what action strategies do you consider most effective to protect this population?"

The first round involved voting on several pre-identified indicators through an online form. Additionally, experts were given the opportunity to suggest new indicators they considered significant through a text box integrated into the questionnaire. These indicators were subsequently analyzed through thematic analysis.[21]

Three reviewers conducted the content analysis. Open-ended questions were organized by topic, allowing for a structured segmentation of responses. To minimize potential interpretation biases, participants were instructed in advance to provide open-ended responses in a bullet-point format. The extraction of emerging indicators followed an inductive approach, where indicators were identified based on the topics mentioned by the experts.

During the second round, the distribution of votes was graphically represented for the indicators that did not achieve previous consensus as well as for the new indicators previously generated. Experts had the opportunity to maintain or adjust their level of agreement regarding the indicators that lacked consensus and to vote on the new indicators.

The process of the second round was repeated in a third and final round, including the indicators recently added. The results of each round were consistently shared with the group anonymously to mitigate any potential biases stemming from experts' apprehension about their opinions being negatively perceived or influenced by personal factors.[20] The Delphi panel started on November 11th, 2023, and the response time ended on January 8th, 2024. The strategies used to minimize attrition rates between rounds included: (i) a clear communication, ensuring participants are well-informed about the study's purpose, procedures, and the

importance of their continued participation; (ii) regular reminders, sending timely reminders to participants about upcoming rounds and deadlines; (iii) feedback, providing participants with feedback on the results of each round to maintain engagement and interest; and (iv) flexibility, allowing flexible deadlines and accommodating participants' schedules to reduce dropout rates.

Data analysis

A consensus threshold of 65% agreement was established for each indicator and applied to the total sample, requiring at least 65% concurrence among responses.[22] This level of consensus can be achieved at any response level, including the options: "totally agree", "agree", "neither agree nor disagree", "disagree", and "totally disagree".

The software used for data analysis and graph generation was Microsoft Excel®.

RESULTS
Composition of the expert panel and response rate

The first round of the panel received 45 responses, meaning that 45 experts agreed to participate in the study. The panel consisted of 32 physicians, including 11 from Infectious Diseases, three from Neurology, one from Immuno-Allergology, seven from Nephrology, two from Internal Medicine, four from Rheumatology, two from Pulmonology, and two from Hematology. Additionally, the panel included two health managers, seven policymakers and consultants, one public health specialist, two members of medical societies, and one member of a patient association.

The second round received 37 responses, reflecting a response rate of 82.2% from the previous round. The third round received 36 responses, representing a 97.3% response rate from the second round.

Overall, a retention rate of 80% was achieved in all three rounds. This is a valid retention rate for studies of this nature, demonstrating the effectiveness of the strategies employed to minimize attrition.[22]

General results for analyzed indicators

Sixty indicators were identified for this Delphi panel based on the preceding qualitative phase. Following the first round of voting, a content analysis identified 29 additional indicators contributed by experts, resulting in a total of 89 indicators, as detailed in Table 1. The complete list of indicators analyzed by the experts can be found in Appendix 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/9949/15716).

By the end of the third round, consensus was achieved for 23 out of the 89 indicators submitted for voting. The predominant level of agreement is in the "strongly agree" category. Of these 23 consensus indicators, eight pertain to Q1, five to Q2, two to Q3 and eight to Q4. Indicators for Q3 only reached consensus in the final round of voting, and specifically in the "agree" category (Figs. 1 to 4).
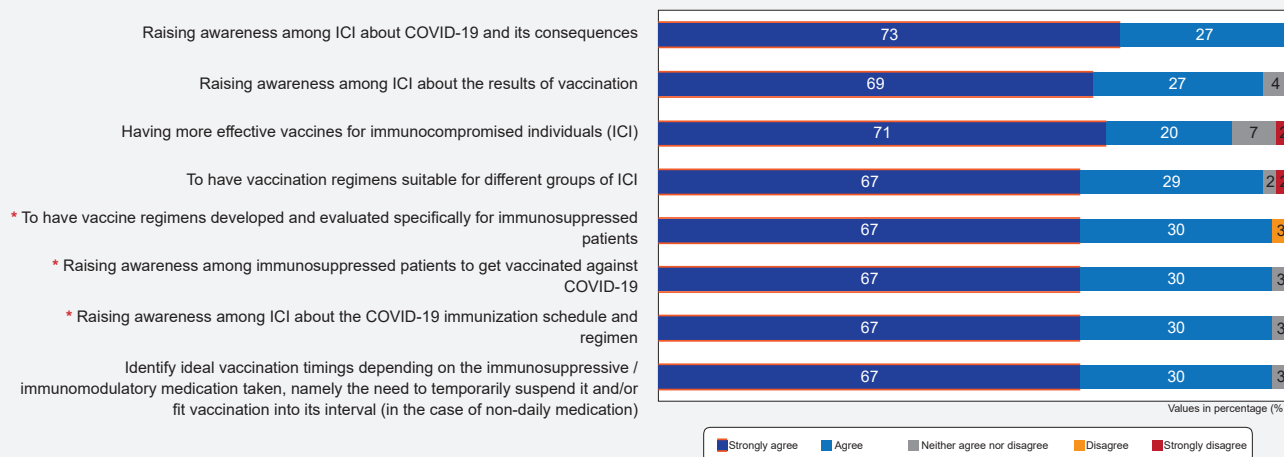
Unmet needs in COVID-19 prevention for ICI

Consensus was been reached on eight out of the 26 indicators related to unmet needs in COVID-19 prevention in ICI, always in the "strongly agree" category (Fig. 1). Consensus indicators were the following: (1) "raising awareness among ICI about COVID-19 and its consequences" (73% strongly agree), (2) "having more effective vaccines for ICI" (71% strongly agree), (3) "raising awareness among ICI about the results of vaccination" (69% strongly agree), (4) "to have vaccine regimens developed and evaluated specifically for immunosuppressed patients" (68% strongly agree), (5) "raising awareness among immunosuppressed patients to get vaccinated against COVID-19" (68% strongly agree), (6) "raising awareness among ICI about the COVID-19 immunization schedule and regimen" (68% strongly agree), (7) "identify ideal vaccination timings depending on the immunosuppressive/immunomodulatory medication taken, namely the need to temporarily suspend it and/or fit vaccination into its interval (in the case of non-daily medication)" (68% strongly agree) and (8) "to have vaccination regimens suitable for different

Table 1 – Indicators according to round, question, and total

		Indicators (n)	
		First round	Second round
Q.1.	To identify unmet needs in COVID-19 prevention in ICI, based on perceptions and clinical experience, to inform and develop effective prevention measures for this vulnerable population.	9	+17
Q.2.	To identify the characteristics that distinguish ICI as a susceptible group in terms of COVID-19.	13	+7
Q.3.	To determine the main outcomes of COVID-19 in ICI.	24	+1
Q.4.	To indicate the most effective action plans for protecting ICI.	13	+4
		60	29
		Total: 89	

Unmet needs in COVID-19 prevention for ICI

Figure 1 – Consensus regarding unmet needs in COVID-19 prevention for ICI. Frequencies corresponding to the level of agreement among consensus indicators (highlighted borders) regarding the unmet needs in COVID-19 prevention for ICI. Results correspond to answers to the question "In your perception, based on your clinical practice, management experience or contact with associates, what needs remain to be met in the prevention of COVID-19 in immunocompromised individuals (ICI)?"
* Indicators added by experts in the second round.

groups of ICI" (67% strongly agree) (Fig. 1). The indicators that did not reach consensus are shown in Appendix 2, Fig. A (Appendix 2: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/9949/15717).

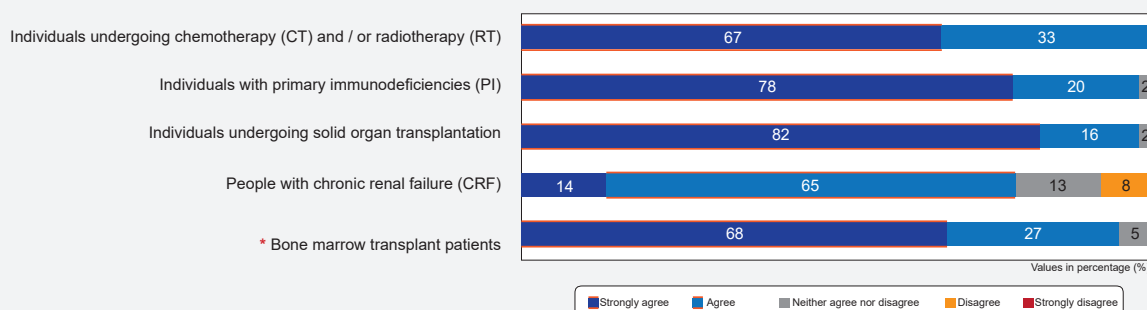### ICI characteristics related to COVID-19 susceptibility

Considering the characteristics of ICI, 20 indicators were identified as being related to COVID-19 susceptibility. Among these, only five achieved consensus among the expert panel, reaching agreement at the following levels: (1) "individuals undergoing solid organ transplantation" (82% strongly agree), (2) "individuals with primary immunodeficiencies (PID)" (78% strongly agree), (3) "bone marrow transplant patients" (68% strongly agree), (4) "individuals undergoing chemotherapy (CT) and/or radiotherapy (RT)" (67% strongly agree) and (5) "individuals with chronic renal failure (CRF)" (65% agree) (Fig. 2). The indicators that did not reach consensus are shown in Appendix 2, Fig. B (Appendix 2: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/9949/15717).

Main outcomes of COVID-19 in ICI

Regarding the main outcomes of COVID-19 in the immunocompromised population, consensus was reached on only 2 of the 25 indicators. Consensus on this issue was not reached until the third round. The indicators with their

ICI characteristics related to COVID-19 susceptibility

Figure 2 – Consensus regarding ICI characteristics related to COVID 19 susceptibility. Frequencies corresponding to the level of agreement among consensus indicators (highlighted borders) regarding ICI characteristics related to COVID-19 susceptibility. Results correspond to answers to the question "Who do you consider to be immunocompromised individuals (ICI), i.e. which ICI characteristics are related to COVID 19 susceptibility?"
* Indicators added by experts in the second round.

corresponding levels of agreement are as follows: (1) "existence of an improvement in the current situation compared to the past, regarding the clinical outcomes of COVID-19" (72% agree) and (2) "existence of an improvement in the current situation compared to the past regarding hospitalizations" (69% agree) (Fig. 3). The indicators that did not reach consensus are shown in Appendix 2, Fig. C (Appendix 2: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/9949/15717).

Action strategies for COVID-19 prevention in ICI

Concerning the most effective action strategies for COVID-19 prevention in ICI, 8 of the 17 indicators have reached consensus. All these indicators achieved the level of agreement in the "strongly agree" category, as follows: (1) "maintaining epidemiological surveillance of COVID-19" (80% strongly agree), (2) "promote health literacy on COVID-19 and vaccination among the immunocompromised

population" (73% strongly agree), (3) "promote the use of measures to prevent the transmission of infection (hand washing) among ICI" (73% strongly agree), (4) "promote vaccination in ICI" (73% strongly agree), (5) "maintain investment (research) in vaccination: more effective and specific vaccines" (73% strongly agree), (6) "prioritize access for ICI to vaccination or drugs that provide greater protection" (70% strongly agree), (7) "facilitate the chain, from prescription to administration, of effective therapies for the prevention of infection (prophylaxis)" (69% strongly agree) and (8) "action strategies aimed at different sub-groups of ICI, groups that are more homogeneous (e.g. distinguishing different levels of severity; of need for intervention depending on this assessment of severity; of the pathology and the medication taken)" (67% strongly agree) (Fig. 4). The indicators that did not reach consensus are shown in Appendix 2, Fig. D (Appendix 2: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/9949/15717).
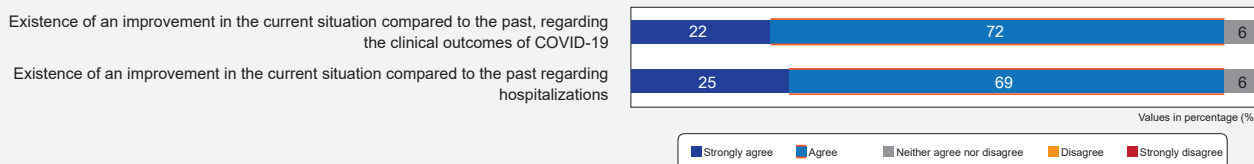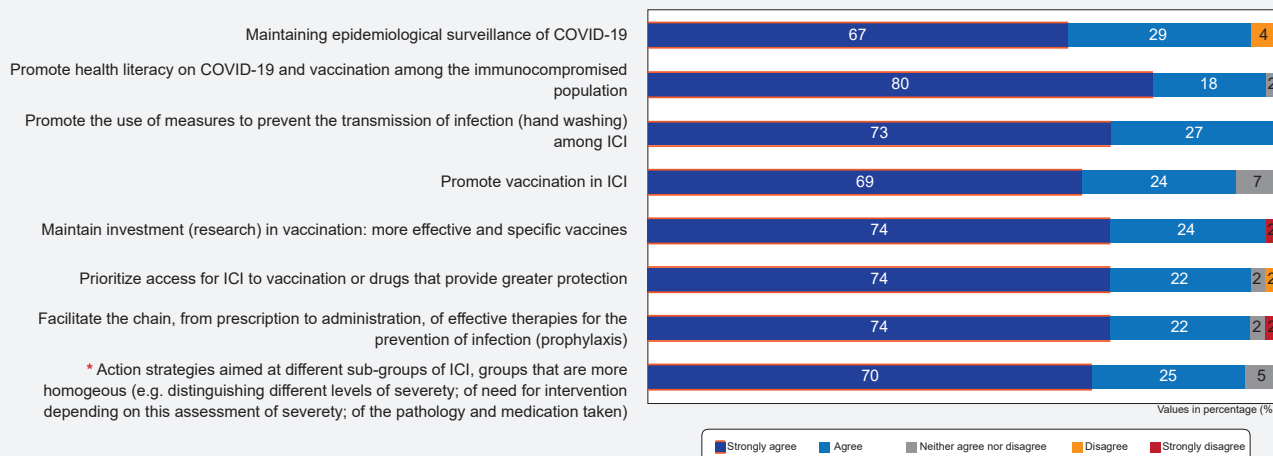

Figure 3 – Consensus regarding main outcomes of COVID-19 in ICI. Frequencies corresponding to the level of agreement among consensus indicators (highlighted borders) regarding the main outcomes of COVID-19 in ICI. Results correspond to answers to the question "Currently, in your perception, what do you consider to be the main outcomes of COVID-19 in immunocompromised individuals (ICI)?"
* Indicators added by experts in the second round.

Figure 4 – Consensus regarding action strategies for COVID-19 prevention in ICI. Frequencies corresponding to the level of agreement among consensus indicators (highlighted borders) regarding the action strategies for COVID-19 prevention in ICI. Results correspond to answers to the question "Regarding the need to prevent COVID-19 in immunocompromised individuals (ICI), what action strategies do you consider most effective to protect this population?"
* Indicators added by experts in the second round.

DISCUSSION

This Delphi panel study comprehensively examined key indicators for preventing and managing COVID-19 in ICI using a broad and multidisciplinary panel of experts. In total, our expert panel identified 89 indicators in four different dimensions of the ICI and COVID-19 context. Though only 23 of such indicators reached consensus, which indicates a possible divergence in the experts' approaches or, in some cases, the need for more scientific evidence, the substantial agreement obtained in the "strongly agree" category underlines the experts' robust alignment on the consensus indicators.

Regarding the unmet needs in COVID-19 prevention for the immunocompromised population, the thematic prioritization of the consensualized results highlights several key areas needing attention. These include raising awareness about the disease and vaccination outcomes among ICI, ensuring their safety and understanding, and the urgent need for targeted vaccination strategies tailored to this population. This focus includes developing more effective vaccines and personalized immunization schedules that accommodate diverse health conditions and treatment regimens, as well as raising awareness of preventative measures to reduce vaccine hesitancy. These results align with existing scientific evidence,[23–27] emphasizing the need for optimized preventive strategies for ICI. To achieve the maximum level of protection, other authors also add that these strategies should consider the type of vaccine used, dosage regimens, and the possibility of additional doses or revaccinations.[3,28] Furthermore, other authors suggest additional measures to complement suboptimal vaccine response, such as the use of monoclonal antibodies,[3,6,24,29] which was an indicator that obtained 56 percent agreement in our panel (9% short of consensus on the "strongly agree" category) [Appendix 2, Fig. A (Appendix 2: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/9949/15717)]. Hence, ICI face significant challenges in achieving adequate immune responses to COVID-19 vaccination, rendering them more susceptible to severe outcomes.[24,30,31] Addressing these challenges is considered essential to safeguarding ICI and mitigating the impact of COVID-19 on their health and healthcare systems.[25,29]

The identification of ICI characteristics related to COVID-19 susceptibility emerged as another significant point in this analysis. Although 20 indicators were identified, consensus was achieved on only five, highlighting the complexity of defining this population and respective subsets.[25,32] This expert divergence pinpoints the consequent challenges in developing universally applicable strategies for COVID-19 prevention and management, particularly in such diverse population subsets. According to our panel of experts, individuals undergoing chemotherapy or radiotherapy, those

with primary immunodeficiencies, solid organ transplant recipients, individuals with chronic kidney disease, and bone marrow transplant recipients are identified as susceptible groups in terms of COVID-19. This characterization is corroborated by other authors, who have also identified these individuals as being at greater risk of developing serious complications and dying due to COVID-19.[9,33–35] Besides their immunocompromised status, these individuals often have advanced age and other comorbidities, further increasing their risk for poor outcomes.[9,36–40]

The clinical characteristics and outcomes of COVID-19 in ICI, who are believed to be at higher risk for severe disease but may also have reduced inflammatory responses, are not well defined.[33] Thus, more evidence is needed to determine the risk attributable to immunocompromising conditions and therapies for the prognosis of COVID-19.[34]

Regarding outcomes associated with COVID-19, experts found improvements in clinical results and a reduction in hospitalizations compared to the past (Fig. 3). These findings can be further contextualized in relation to the core outcome set (COS) for post-COVID-19 condition, as developed by Gorst *et al*.[41] This COS provides a standardized framework for assessing key health outcomes in post-COVID-19 patients, including fatigue, respiratory symptoms, cognitive dysfunction, and recovery measures.[41] Some of these indicators align with the vulnerabilities identified for ICI in our study, particularly the need for continuous monitoring and improved treatment accessibility.[41] However, while the COS broadly addresses post-COVID-19 outcomes, it does not fully capture the specific challenges faced by ICI, such as vaccine response limitations and a heightened risk of severe disease progression.[41] Future research should examine how these core outcomes can be adapted to better reflect the distinct health risks of ICI, ensuring that prevention strategies remain aligned with internationally recommended measures while addressing the unique vulnerabilities of this high-risk population. Although several experts emphasized the ongoing need to focus on reducing severe cases and subsequent hospitalizations, there was no consensus on this point. The limited agreement on COVID-19 outcome indicators – only two consensual out of 25 identified –suggests significant heterogeneity in expert opinions. While improvements in clinical conditions and reduced hospitalizations are positive signs, the lack of consensus on more indicators may reflect variations in clinical experience among experts or the need for more comprehensive scientific evidence.[42] This highlights the complexity of assessing COVID-19 outcomes in ICI and reinforces the need for targeted preventive measures.[43]

Furthermore, our results also emphasize the importance of disease monitoring and health literacy promotion in COVID-19 prevention strategies. The consensus reached

on the eight related indicators aligns with the unmet needs identified in this panel, highlighting the need to maintain epidemiological surveillance and drive forward health literacy initiatives among ICI and the wider public. Additionally, tailored educational strategies for specific subgroups of immunocompromised individuals, along with initiatives to enhance access to effective immunization strategies and therapies, were identified as crucial consensual strategies. These strategies are also consistent with existing evidence.[24,35,44,45]

Finally, experts have identified key research priorities, including the development of effective therapies, more immunization strategies, and treatments for viral infections in ICI. These research opportunities are crucial, as they aim to improve both health outcomes and quality of life of people with ICI.[9,45] As COVID-19 transitions from pandemic to endemic status, establishing effective health measures remains imperative to protect ICI from ongoing infectious threats.[24]

Strengths and limitations

One aspect of the study was the lack of consensus on many indicators. This outcome likely reflects the diversity of backgrounds, perspectives, and prioritizations among the experts involved, which led to differing opinions and interpretations of the pre-identified and generated indicators. Given the complexity of the topic and the inherent subjectivity in evaluating certain indicators, particularly those for which robust scientific evidence is still limited, some degree of divergence was expected. Rather than weakening the study, these differing perspectives contributed to a valuable discussion and helped identify areas where further research and clarification are necessary.

Although individual patients were not directly involved in the expert panel, the study incorporated specialists representing patient advocacy groups. This ensured that patient perspectives and priorities were considered in the evaluation of indicators, even if indirectly. The inclusion of these representatives strengthened the applicability of the findings by bridging clinical expertise with the lived experiences of the affected population.

The questions formulated to perform the Delphi panel were informed primarily by literature review and expert consultation, a widely accepted approach for developing indicators in consensus studies. These methods ensure that the questions reflect practical and field-relevant insights. While expert input alone may involve some inherent subjectivity, it remains a robust and appropriate method for this type of research.

Additionally, while the study did not explicitly control for regional representation or sex balance, the diversity of expertise within the panel ensured a broad and well-informed

discussion. This approach strengthens the overall applicability of the findings.

Given that the response rate remained within the recommended range throughout the three Delphi panel rounds, it is also reasonable to conclude that the experts' responses were motivated by a genuine interest in the topic, thereby reducing potential bias. In addition, the inclusion of a significant number of specialists in this expert panel enriched the variability of perspectives, thereby strengthening the results.

To preserve confidentiality and anonymity, specific details regarding the identities and affiliations of the experts were intentionally excluded from the manuscript. Addressing these methodological considerations and maintaining transparency yielded valuable insights and actionable strategies from a diverse panel of experts. These findings offer crucial guidance for improving COVID-19 prevention strategies for ICI, highlighting gaps, and providing expert recommendations for safeguarding this vulnerable population.

CONCLUSION

In conclusion, this study highlights the critical need for tailored COVID-19 prevention and management strategies for ICI in Portugal. Through the Delphi panel methodology, 89 key indicators were identified, with consensus reached on 23 of them, revealing essential areas for intervention. The findings emphasize the importance of raising awareness among ICI about COVID-19 and vaccination, developing immunization strategies tailored to their specific conditions, and identifying optimal vaccination regimens for this population.

The study also underscores the necessity of strengthening epidemiological surveillance and promoting health literacy to enhance preventive measures. Experts reached consensus on the importance of maintaining continuous monitoring of COVID-19, ensuring access to accurate information, and implementing targeted educational strategies to reduce vaccine hesitancy and increase adherence to protective measures. Additionally, investment in research remains essential to develop more effective vaccines and therapeutic options specifically suited for ICI.

Regarding the outcomes of COVID-19 in ICI, consensus was reached on the perception that there have been improvements in clinical outcomes and hospitalization rates compared to the past. However, the lack of consensus on several other indicators suggests a need for further research to better define the risks and prognosis of COVID-19 in this population.

Furthermore, experts strongly agreed on the need for a structured approach to COVID-19 prevention in ICI, which includes maintaining access to vaccination and prophylactic treatments, prioritizing ICI in public health strategies, and

tailoring prevention measures based on different immuno-suppressive conditions. The study reinforces the importance of collaboration between healthcare professionals, policymakers, and patient associations to effectively implement these strategies.

Given the persistent presence of SARS-CoV-2 and the risk of new variants, continuous efforts to safeguard immuno-compromised individuals remain crucial. The insights obtained in this study provide a foundation for future discussions and policy development, aiming to optimize COVID-19 prevention strategies for ICI in Portugal and address existing gaps in their protection and care.

AUTHOR CONTRIBUTIONS

ASC, BR, ARP: Study conception and design; study conduction, the analysis and interpretation of the results; first draft of the manuscript, and all authors edited, reviewed, and approved the final version of the manuscript.

JVC: First draft of the manuscript, and all authors edited, reviewed, and approved the final version of the manuscript.

MJM: Study conception and design; final version of the manuscript revision, with important contributions to the discussion.

All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in October 2024.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

MJM is employed by AstraZeneca.

All other authors have declared that no competing interests exist.

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