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Post COVID-19 pandemic Inflammatory Insights into Cancer: Consequences for immunotherapy

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ABSTRACT

The COVID-19 pandemic has reshaped the landscape of global health, revealing novel interactions between infectious diseases and chronic conditions such as cancer. Beyond acute infection, growing evidence suggests that persistent exposure to SARS-CoV-2 spike protein, whether through infection or vaccination, may sustain inflammatory pathways that contribute to tumour progression and immune modulation. This review explores the overlap between post-COVID inflammation, particularly in Long-COVID syndromes and the tumour microenvironment (TME), focusing on key mediators such as IL-6, TNF-α, IL-1β, and NF-κB. We revisit the concept of the cytokine storm in the context of persistent inflammation, spike protein immunogenicity and immune exhaustion, proposing a model in which chronic inflammatory signalling may disrupt tumour immune surveillance, reawaken dormant cancer cells and compromise the efficacy of immunotherapies. Comparative analysis with other cancer types highlights shared pathways of oncogenic inflammation. Lastly, we outline emerging therapeutic strategies to mitigate these effects, including cytokine-targeted interventions and immunomodulatory screening in post-COVID cancer patients. These post-pandemic insights call for urgent translational research to ensure effective and safe cancer immunotherapy in the evolving inflammatory landscape.

1. Introduction

The COVID-19 pandemic has left a persistent and multifaceted legacy on global health, with one of the most consequential effects being long-term immune dysregulation. While most of the initial focus during the acute phases of the pandemic centered around respiratory pathology and systemic inflammatory responses, research is now uncovering the chronic consequences of SARS-CoV-2 infection. It is within this evolving landscape that we revisit and extend the observation made in our previous review article, "Cancer and COVID-19: Collectively Catastrophic" [1], where we outlined the initial pathophysiological overlap between SARS-CoV-2-induced inflammation and cancer progression, emphasizing acute-phase mechanisms and shared cytokine pathways. However, as the pandemic has transitioned into an endemic phase and Long-COVID has emerged as a clinical reality, novel considerations now demand urgent attention. These include persistent immune activation, cytokine imbalances, reactivation of latent infections, and tissue-specific inflammation, collectively termed post-acute sequelae of SARS-CoV-2 infection (PASC), or more commonly, Long-COVID [2]. Long-COVID is a chronic condition characterized by a collection of health problems that persist for three months or longer after an initial SARS-CoV-2 infection. These symptoms can include fatigue, brain fog, shortness of breath, headaches, changes in smell or taste and can affect various body systems. Additionally, cancer survivors are observed to have higher odds of developing Long-COVID, particularly younger survivors [3].

Central to these prolonged effects is the persistence of the SARS-CoV-2 spike protein, which has been detected in various tissues and immune cells for months following infection or vaccination, even in the absence of replicating virus [4–7]. The spike protein is a potent immunogen,

Abbreviations: **DCC,**, dormant cancer cells; **HIF-1,**, hypoxia inducible factor 1; **ICI,**, immune checkpoint inhibitor; **LAG3,**, lymphocyte activation gene-3; **MDP,**, monocyte differentiation program; **NCM,**, non-classical monocyte; **PASC,**, post-acute sequelae of SARS-CoV-2; **TIGIT,**, T cell immunoreceptor with Ig and ITIM domains; **TME,**, Tumour microenvironment.

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capable of activating innate immune receptors such as toll-like receptors (TLRs), promoting NF-κB signalling, and stimulating proinflammatory cytokine release, including interleukin-6 (IL-6), IL-1β, and tumour necrosis factor-alpha (TNF-α) [8–11]. This low-grade, sustained inflammatory response may contribute to chronic symptoms in Long-COVID and has also been proposed to modulate the course of other diseases, including cancer [12].

Cancer and chronic inflammation are closely intertwined. Tumour development and progression are often associated with an inflammatory tumour microenvironment (TME), characterized by the recruitment of immune cells, dysregulated cytokine signalling and immune evasion mechanisms [13,14]. In this context, a pre-existing inflammatory state, as seen in Long-COVID, may significantly influence tumour biology and therapeutic response. This is particularly relevant for patients receiving cancer immunotherapy, such as immune checkpoint inhibitors (ICIs), which rely on restoring or enhancing immune surveillance to achieve tumour control [15].

The balance between effective anti-tumour immunity and immune-related adverse effects is delicate and may be disrupted by COVID-induced or post-vaccination inflammatory perturbations. For example, chronic elevation of IL-6 and other cytokines implicated in both COVID-19 and tumour progression (such as IL-1β, TNF-α, IFN-γ) may alter T cell function, myeloid-derived suppressor cell recruitment and dendritic cell priming, all of which are crucial to immunotherapy efficacy [16,17].

Emerging evidence suggests that SARS-CoV-2 infection may exert long-term oncological effects. Notably, the virus has been implicated in the reactivation of dormant cancer cells through epigenetic remodelling and metabolic reprogramming [18], raising concerns regarding tumour recurrence among cancer survivors with Long-COVID. Although most clinical cohort studies report that patients with breast cancer and mild COVID-19 are not at significantly elevated risk of adverse outcomes [19,20], mechanistic investigations reveal a more intricate relationship. For example, a prospective registry analysis indicated that COVID-19 related mortality in breast cancer patients was primarily associated with pre-existing comorbidities rather than prior radiation therapy or ongoing anti-cancer treatment [20]. Collectively, these findings underscore that the persistence of viral antigens within the TME may activate pro-tumorigenic signalling pathways, potentially compromising tumour control and diminishing the efficacy and safety of immunotherapeutic interventions.

This review highlights recent advances in our understanding of post-COVID inflammatory responses and their implications for cancer immunotherapy, drawing on clinical, immunological, and molecular insights. We propose that chronic exposure to spike protein and Long-COVID-related immune dysfunction should be considered when evaluating cancer progression and treatment responses, particularly in immunotherapy treated populations.

2. Revisiting the cytokine storm and its shared mechanisms with cancer

During acute SARS-CoV-2 infection, the immune system can become hyperactivated, resulting in a cytokine storm, a systemic inflammatory response marked by elevated levels of IL-6, IL-1β, TNF-α, and IFN-γ as mentioned previously [21,22]. These cytokines not only contribute to acute morbidity and mortality through vascular leakage, endothelial injury, and multi-organ failure [23], but they also mirror cytokine profiles observed in various cancers, particularly those with a highly inflamed TME, such as triple-negative breast cancer (TNBC) [16].

The TME is a complex niche composed of tumour cells, stromal cells, immune infiltrates, and a cytokine-rich extracellular matrix. It is shaped by both intrinsic tumour signals and extrinsic inflammatory cues [24]. Notably, many of the same cytokines central to the COVID-19 cytokine storm also shape the immunosuppressive and tumour-promoting landscape of the TME [14,25]. For example, IL-6 is a key driver of tumour growth, angiogenesis, and epithelial-mesenchymal transition (EMT), while TNF-α and IL-1β contribute to the recruitment of myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs), reinforcing immune evasion [26].

At the molecular level, both COVID-19-related inflammation and cancer progression converge on common signalling pathways, notably NF-κB and IL-6/JAK/STAT3. Spike protein activation of TLR4 triggers these cascades, contributing to cytokine production and immune modulation [27–30]. These shared mechanisms directly relate to immunotherapy response, especially via programmed death-ligand 1 (PD-L1) upregulation and resistance development.

Tyagi et al. (2025) emphasize that, beyond triggering cytokine cascades, SARS-CoV-2 can remodel the TME via NETosis, oxidative stress, and tissue hypoxia. Neutrophil extracellular traps (NETs) which are web-like structures of extracellular DNA and proteases released by neutrophils, promote tumour invasion and immune evasion, while reactive oxygen species (ROS) drive genomic instability and suppress antitumour immunity. Hypoxia stabilizes hypoxia inducing factor 1-alpha (HIF-1α), leading to PD-L1 upregulation and immune checkpoint resistance. Targeting these pathways with NETosis inhibitors (for example DNase and Peptidylarginine deiminase 4 (PAD4) inhibitors), ROS scavengers, and HIF-1α antagonists could mitigate these effects and improve immunotherapy outcomes in post-COVID cancer patients [31]. These interconnected inflammatory and immunosuppressive pathways are summarized in Fig. 1. Collectively, these immunological and metabolic shifts not only compromise tumour immune surveillance but may also serve as triggers for reactivating dormant tumour cells, a key focus of the following section.

3. Long-COVID, tumour dormancy and immune escape

3.1. Immunological landscape of long-COVID

Beyond acute infection, Long-COVID, or PASC, is characterized by persistent symptoms such as fatigue, neurocognitive deficits, and ongoing inflammation, affecting up to 30 % of patients even after mild initial disease [2]. Immune profiling of Long-COVID cohorts reveals elevated levels of cytokines such as IL-6, IL-1β, VEGF, and TNF-α, alongside increased T cell exhaustion markers and elevated monocyte counts [32]. Guerrera and authors observed that in COVID-19 patients, depletion of multiple innate immune cell subsets was observed, including plasmacytoid and conventional dendritic cells, classical, non-classical, and intermediate monocytes, as well as monocyte-derived inflammatory dendritic cells. Basal inflammation levels were higher in COVID-19 patients than in those with Long-COVID, whose immune profiles more closely resembled those of healthy donors and recovered individuals. Nonetheless, Long-COVID patients exhibited persistent immune alterations, characterised by reduced frequencies of $CD4^+$ and $CD8^+$ T cells, Tregs and switched memory B cells, mirroring patterns seen in acute COVID-19 [33]. These immune alterations and their downstream effects on tumour dormancy disruption and immune escape are illustrated in Fig. 2. Furthermore, these immunological alterations closely resemble the immunosuppressive TME often observed in cancers such as breast, ovarian, and colorectal malignancies [34].

3.2. Mechanistic links between long-COVID and tumour progression

Long-COVID may impair tumour immune surveillance through metabolic reprogramming and the reactivation of dormant cancer cells (DCCs). SARS-CoV-2 infection has been demonstrated to induce a metabolic shift in host cells, characterized by reduced mitochondrial oxidative phosphorylation and increased glycolysis, a phenomenon referred to as the "Warburg effect" in cancer biology [35]. This metabolic rewiring is not limited to infected host cells but extends to immune cells within the TME, leading to dysfunctional immune responses. For example, effector T cells rely on glycolysis for activation, but chronic metabolic stress and altered nutrient availability can induce T cell

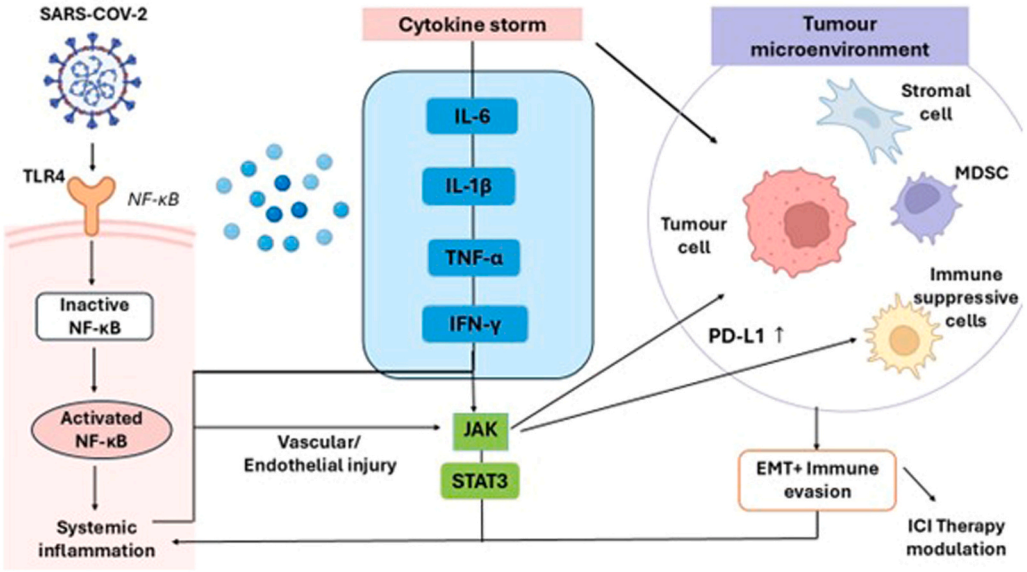

Fig. 1. Shared inflammatory mechanisms between COVID-19 and cancer. SARS-CoV-2 spike protein binding to TLR4 triggers NF-κB activation and release of cytokines (IL-6, IL-1β, TNF-α, IFN-γ), resulting in systemic inflammation and endothelial injury. These cytokines shape the tumour microenvironment by recruiting immunosuppressive cells (MDSCs, Tregs), promoting EMT, activating IL-6/JAK/STAT3 signalling, and increasing PD-L1 expression, which modulates response to immune checkpoint inhibitors (ICIs).

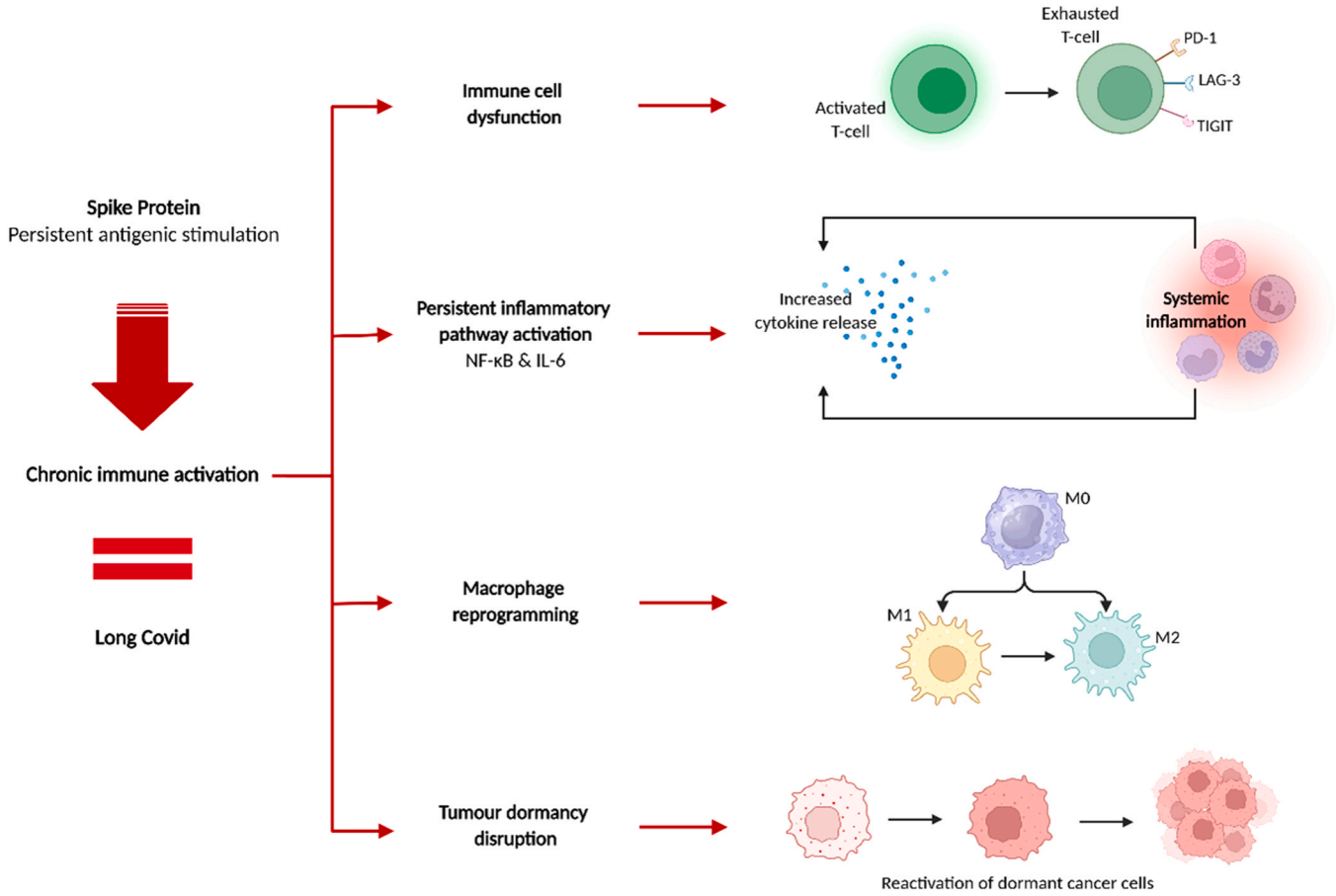

Fig. 2. Chronic immune activation and tumour dormancy disruption in Long-COVID. The persistent antigenic stimulation by the SARS-CoV-2 spike protein leads to immune cell dysfunction, persistent inflammatory pathway activation involving NF-κB and IL-6, macrophage reprogramming, and systemic inflammation. These processes result in T-cell exhaustion, cytokine release, and disruption of tumour dormancy with reactivation of dormant cancer cells, contributing to metastatic progression.

exhaustion, reducing their capacity to detect and eliminate tumour cells [36]. In cancer, similar metabolic adaptations promote immune evasion, enhance survival under hypoxic conditions, and confer resistance to immune checkpoint inhibitors (ICI's) [37].

Furthermore, persistent inflammation, oxidative stress, and tissue hypoxia, a hallmark of Long-COVID, can disrupt dormancy programs that normally keep disseminated tumour cells in a quiescent state. ROS produced during oxidative stress can activate signalling pathways such as NF-κB and STAT3, which drive dormant cells to re-enter the cell cycle and promote metastatic outgrowth [38]. Additionally, HIF-1α stabilization under hypoxic conditions further exacerbates this process by upregulating genes involved in angiogenesis, autophagy, and metabolic reprogramming, thereby reinforcing tumour progression and survival in hostile microenvironments [39].

This interplay between metabolic dysregulation and immune suppression highlights a critical mechanism by which Long-COVID may increase the risk of cancer recurrence and progression, suggesting that targeting metabolic pathways could be a promising therapeutic strategy in post-COVID oncology care.

3.3. *Inflammatory and viral triggers of dormancy escape*

Persistent elevation of pro-inflammatory cytokines such as IL-6 and IL-1β in Long-COVID patients can significantly influence tumour biology by activating critical signalling pathways including STAT3, NF-κB, and HIF-1α. These pathways are well-documented drivers of tumour cell proliferation, angiogenesis, and escape from dormancy, contributing to metastatic progression [40]. For example, STAT3 activation promotes transcription of genes involved in cell cycle progression and survival, while NF-κB signalling orchestrates inflammatory responses that reshape the TME to favour cancer cell reawakening. Furthermore, inflammation associated with COVID-19 can reactivate dormant breast cancer cells, promoting metastatic outgrowth through these inflammatory cascades [18].

Long-COVID has also been associated with the reactivation of latent viral infections such as Epstein–Barr virus (EBV) and human endogenous retroviruses (HERVs) [41]. EBV reactivation has been implicated in various cancers through mechanisms involving immune evasion, chronic inflammation, and direct oncogenic effects. Similarly, HERV activation can modulate immune recognition and has been linked to tumorigenesis in susceptible individuals by altering gene expression and promoting a pro-inflammatory milieu [42]. The convergence of viral reactivation with sustained cytokine-driven inflammation in Long-COVID patients may therefore synergistically disrupt immune surveillance, facilitate tumour dormancy escape and enhance metastatic risk.

3.4. *Therapeutic and research implications*

The convergence of inflammatory reactivation, mitochondrial dysfunction and viral persistence establishes a permissive microenvironment for tumour progression, particularly among cancer survivors. This interplay may disrupt cellular homeostasis, promote oxidative stress and sustain pro-survival signalling pathways that facilitate tumour cell reawakening. Understanding these mechanisms opens avenues for therapeutic intervention, including the use of ROS scavengers to mitigate oxidative stress, HIF-1α antagonists to counter hypoxia-driven metabolic reprogramming and targeted anti-inflammatory agents to restore immune balance [43]. Integrating such approaches into oncology care could help preserve tumour dormancy and enhance patient outcomes, particularly in the context of COVID-19 associated immune dysregulation. As the long-term effects of SARS-CoV-2 on cancer biology continue to unfold, longitudinal studies are urgently needed to evaluate recurrence risk in cancer survivors with a history of Long-COVID, with particular attention to those receiving ICIs or other immunomodulatory therapies.

4. Persistent SARS-CoV-2 antigen exposure and immune dysregulation

SARS-CoV-2 spike protein, an immunogenic transmembrane glycoprotein, has been detected in plasma and peripheral blood mononuclear cells (PBMCs) for up to one year following infection or vaccination, particularly in patients experiencing Long-COVID [4,5]. This persistence can occur even in the absence of detectable viral RNA, suggesting sustained antigenic stimulation capable of maintaining chronic immune activation through NF-κB and IL-6 signalling pathways [44].

Long-COVID is characterized by persistent immune dysregulation, including elevated inflammatory cytokines, T cell exhaustion, and impaired immune cell function. T cell exhaustion, a hallmark of chronic viral infections, is defined by increased expression of inhibitory receptors such as PD-1, lymphocyte activation gene-3 (LAG-3), and T cell immunoreceptor with Ig and ITIM domains (TIGIT) [32,45]. Exhausted T cells exhibit reduced cytotoxicity and cytokine production, compromising effective anti-tumour responses and potentially diminishing the efficacy of ICIs [46].

Macrophage activation and polarization further modulate immune responses. Long-COVID associated macrophage reprogramming can shift the balance toward pro-inflammatory M1 or immunosuppressive M2 phenotypes, either enhancing or dampening ICI efficacy depending on the dominant phenotype [47]. Emerging evidence also highlights immunometabolic reprogramming in Long-COVID, including glycolytic shifts and mitochondrial dysfunction in immune cells, which mirror the metabolic states of exhausted T cells and tumour-associated macrophages (TAMs) in the TME. These alterations impair antigen presentation, cytokine production, and cytotoxic function, collectively undermining tumour immune surveillance [27].

The convergence of persistent antigen exposure, immune exhaustion, and immunometabolic dysregulation provides a mechanistic rationale for considering metabolic modulators, such as mitochondrial enhancers or glycolysis inhibitors, as adjuncts to immunotherapy. Targeting these pathways may restore immune competence and improve therapeutic outcomes in patients with prolonged post-viral inflammation.

5. Implications for cancer immunotherapy

Persistent immune activation driven by spike protein and Long-COVID-associated dysregulation has important implications for ICIs, which depend on a finely tuned balance between immune activation and suppression. Chronic low-grade inflammation and cytokine priming may maintain the immune system in a heightened state of alertness, potentially increasing the risk of immune-related adverse events (irAEs) and cytokine release syndrome (CRS) [48,49].

A study of 121 patients found that 61 (50.4 %) had received immunotherapy within the previous 12 months. COVID-19 related mortality was higher in patients receiving ICIs compared with those on chemotherapy, however, better functional status and prior COVID-19 vaccination were associated with reduced mortality [50]. Evidence remains controversial, as another study reported no increase in irAE rates or differences in survival outcomes between vaccinated and unvaccinated patients. Interestingly, among patients with high PD-L1 expression treated with ICIs alone, vaccination was linked to improved overall survival. The study also concluded that recommended COVID-19 vaccine boosters can be safely administered to patients with advanced non-small cell lung carcinoma (NSCLC) receiving immune checkpoint blockade [51]. In contrast, Sabbatino and authors showed that high soluble PD-L1 (sPD-L1) levels during COVID-19 were associated with low lymphocyte counts, elevated CRP and longer hospital stays, indicating worse outcomes. Dynamic changes in sPD-L1 correlated with recovery patterns, suggesting it may serve as a prognostic biomarker reflecting both immune suppression early and immune regulation later in infection [52]. In another study, in 281 cancer patients with COVID-19, 30-day mortality was 22 % and was associated with older

age, prior radiation, anaemia, and leukocytosis [53]. Immunotherapy did not increase mortality risk, highlighting the importance of individualized risk assessment.

Interestingly, when carefully timed and clinically managed, spike protein–induced immune activation may also enhance anti-tumour immunity. Mild post-vaccination inflammation has been suggested to synergize with ICIs by promoting T cell activation and improving tumour response in select malignancies [54,55]. These findings underscore the potential value of individualized ICI scheduling and inflammatory monitoring using biomarkers such as IL-6 and CRP to maximize efficacy while minimizing toxicity [56,57].

6. Clinical observations of COVID-19 and ICI therapy

The intersection of COVID-19 and ICI therapy has posed several clinical challenges. During early pandemic phases, treatment interruptions were common due to concerns over exacerbating COVID-19 severity. Observational data, however, indicate that short-term delays may not universally compromise outcomes. For example, in patients with head and neck squamous cell carcinoma, ICI response rates were maintained despite treatment delays of up to four months, suggesting resilience in anti-tumour immunity [58].

Meta-analyses of cancer patients with COVID-19 show that prior ICI exposure generally does not increase mortality or ICU admission compared with patients receiving other systemic therapies [59,60]. However, subsets of patients, particularly those with elevated inflammatory markers or recent ICI administration, may be at higher risk for respiratory complications, especially in lung cancer.

COVID-19 vaccination during ICI therapy appears largely safe. Studies in renal cell carcinoma and melanoma have reported no significant increase in severe irAEs, with only mild, self-limiting symptoms observed [61]. Rare case reports have described unexpected severe irAEs, including myocarditis and pneumonitis, following infection or vaccination [62,63], highlighting the potential for heightened immune reactivity in a subset of patients.

These observations emphasize the need for ongoing clinical vigilance. Individualized monitoring of inflammatory markers, careful timing of ICI dosing, and consideration of patients' SARS-CoV-2 exposure history may help mitigate risks. Prospective studies are required to clarify long-term consequences, particularly in patients with autoimmune predispositions or persistent post-viral inflammation. Table 1 summarizes mechanistic insights that often affect ICI outcomes.

7. Therapeutic implications and recommendations

Given the persistent inflammatory milieu associated with spike protein retention and Long-COVID, ICI therapy in cancer patients must be re-evaluated to ensure safety and efficacy in this altered immunological context. Pre-immunotherapy screening is increasingly important, particularly for individuals with a known history of COVID-19 or PCAS. Clinicians should assess biomarkers indicative of persistent inflammation, including CRP, IL-6, and markers of T cell exhaustion such as PD-1 and TIGIT, to gauge the patient's immunological readiness for ICIs [41,73]. Such stratification may allow for better prediction of therapy outcomes and help avoid irAEs in patients with a dysregulated immune baseline.

Table 1
Mechanistic Insights Affecting ICI Outcomes.

Mechanism	Effect on Immunotherapy	References
NF-κB & IL-6/STAT3 Activation	May boost PD-L1 expression but also aggravate inflammation.	[64–66]
T cell Exhaustion & Dysfunction	Limits ICI efficacy; requires T cell rejuvenation strategies.	[46,67,68]
Macrophage Reprogramming	Viral reprogramming (e.g., non-classical monocytes induction) may synergize or compete with ICI action.	[69,70]
Immune Senescence & Inflammaging	Chronic aging-like inflammation reduces ICI effectiveness; anti-inflammatory agents (e.g., IL-1 blockers, JAK inhibitors) are being explored.	[71,72]

The timing of SARS-CoV-2 vaccination relative to ICI administration has also emerged as a critical consideration. While mRNA vaccines are generally safe and effective, their temporary induction of inflammatory responses can intersect with ICI-driven immune activation, potentially exacerbating adverse effects. Therefore, spacing vaccination doses relative to ICI cycles may mitigate overlapping inflammatory peaks, reduce toxicity, and preserve therapeutic benefit [61]. This is especially pertinent for patients on combination immunotherapy regimens or those with known inflammatory co-morbidities.

The therapeutic landscape is evolving to include adjunctive use of anti-inflammatory agents during ICI treatment. Trials involving IL-1 receptor antagonists (e.g., anakinra), JAK inhibitors, and even low-dose antiviral agents are being considered to dampen excessive inflammatory signalling without compromising antitumour immunity [74,75]. These approaches may be particularly beneficial for patients with persistent spike protein presence or Long-COVID, who are at elevated risk of ICI-related toxicity.

An emerging and promising avenue involves harnessing the phenomenon of SARS-CoV-2-induced monocyte reprogramming. Studies have shown that the virus can induce the differentiation of non-classical monocytes (NCMs) with cytotoxic potential, suggesting that viral antigens may inadvertently "train" the innate immune system towards tumoricidal activity [70]. This reprogramming effect opens the door for developing MDP (monocyte differentiation program)-mimetic drugs, which could be used in combination with ICIs to augment response in otherwise immunotherapy-resistant tumours (Fig. 3). These agents could simulate the monocyte-driven immune activation seen in COVID-19, but in a controlled therapeutic context, thereby enhancing antitumour efficacy while minimizing systemic inflammation [49].

A deeper understanding of SARS-CoV-2's immunological aftermath is thus urgently needed to optimize immunotherapy regimens. Integrating biomarker-driven stratification, tailored vaccination schedules, adjunctive anti-inflammatories and novel immunomodulatory strategies will be key in managing cancer patients in the post-pandemic era.

8. Future research directions

The post-pandemic era presents a pressing need to elucidate the long-term immunological consequences of SARS-CoV-2 infection and vaccination in cancer patients, particularly those receiving ICIs. Future research should emphasize prospective, longitudinal studies that systematically monitor inflammatory status, immune checkpoint marker expression and spike protein persistence in patients undergoing immunotherapy. Serial assessments of cytokines (IL-6, IL-1β, TNF-α), T cell exhaustion markers (PD-1, LAG-3, TIM-3, TIGIT) and innate immune cell reprogramming will be essential to clarify how persistent inflammation influences therapeutic efficacy and outcomes.

A critical research priority involves defining how spike protein persistence affects tumour–immune system interactions, especially in patients with pre-existing or active malignancies. Quantifying spike protein levels and correlating them with ICI response, immune-related toxicity and tumour progression could provide valuable insights for biomarker discovery and clinical decision-making. Incorporating spike protein detection into ongoing and future cancer immunotherapy trials will be vital to identify patients at higher risk for irAEs or resistance to therapy.

Given the role of inflammation in modulating ICI response, combination strategies that counteract inflammation-induced resistance deserve focused investigation. Promising approaches include the co-administration of ICIs with anti-inflammatory agents such as IL-1 antagonists (e.g., anakinra), IL-6 inhibitors (e.g., tocilizumab), or JAK

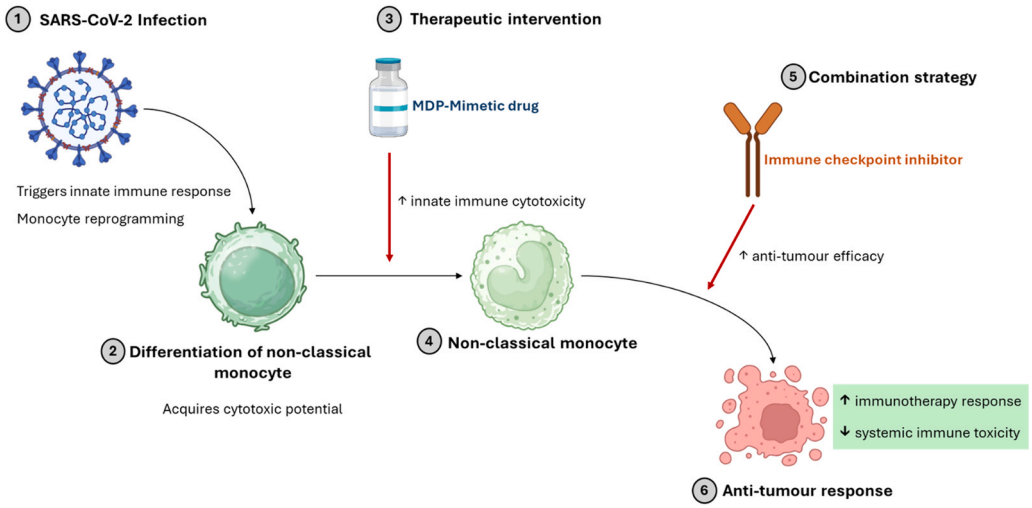

Fig. 3. SARS-CoV-2-induced monocyte reprogramming as a therapeutic avenue in cancer immunotherapy. 1) SARS-CoV-2 Infection: The virus initiates an innate immune response, triggering changes in circulating monocytes; 2) Monocyte Reprogramming: Viral exposure drives the differentiation of classical monocytes into non-classical monocytes (NCMs) with cytotoxic and pro-inflammatory properties; 3) MDP-Mimetic Drug Development: This viral-induced monocyte differentiation can be pharmacologically simulated using monocyte differentiation program (MDP)-mimetic drugs; 4) Trained Immunity in Monocytes: These agents promote the generation of NCMs that retain trained immunity features, contributing to antitumour immune activation; 5) Combination with Immune Checkpoint Inhibitors (ICIs): When combined with ICIs, MDP-mimetics enhance the efficacy of adaptive immune responses, particularly the cytotoxic T cell-mediated tumour attack and 6) Therapeutic Outcome: This combination strategy leads to increased immunotherapy responsiveness while minimizing systemic immune toxicity, representing a promising approach to treat immunotherapy-resistant cancers.

inhibitors as mentioned previously. The immunomodulatory potential of these drugs should be rigorously tested in post-COVID-19 and Long-COVID settings to ensure they can attenuate harmful inflammation without compromising tumour-specific immunity [76–78].

Another emerging avenue involves the design of "viral-mimetic" immunotherapies inspired by SARS-CoV-2-induced monocyte reprogramming. The virus's ability to polarize monocytes into cytotoxic, tumour-killing phenotypes suggests potential for synthetic mimetics or muramyl dipeptide (MDP) analogues that synergize with ICIs to enhance efficacy in resistant tumours. Preclinical studies exploring these concepts in inflammation-associated cancers such as breast and lung tumours are urgently warranted [79].

In parallel, real-world registry data should be leveraged to investigate cancer recurrence, progression and survival outcomes among patients with Long-COVID. Such registries should stratify patients by cancer type, treatment modality, COVID-19 exposure history, and inflammatory biomarker profiles to generate actionable insights for both oncologists and immunologists.

Building on the mechanistic intersections between SARS-CoV-2-induced inflammation and oncogenic signalling, JAK/TYK2 inhibitors (e.g., baricitinib, ruxolitinib) and TLR/MyD88 pathway antagonists have emerged as promising dual-purpose agents with potential applications in both COVID-19 and cancer. These agents may help suppress IL-6/STAT3-mediated inflammation, a pathway frequently activated by persistent spike protein, while preserving anti-tumour immune activity. Combining ICIs with selective JAK inhibition could thus mitigate excessive cytokine signalling that drives irAEs without fully abrogating cytotoxic T cell responses. Similarly, modulation of TLR4/MyD88 signalling, which contributes to NF-κB-driven cytokine production and immune suppression in the TME, may help restore immune equilibrium. Collectively, these insights provide a strong rationale for translational clinical trials testing combined ICI and immunomodulator regimens targeting JAK/STAT and TLR pathways in cancer patients with prior SARS-CoV-2 exposure or Long-COVID.

Looking forward, precision immunotherapy will increasingly depend on the integration of viral exposure history, inflammatory phenotype and immune exhaustion signatures into personalized treatment frameworks. Leveraging established pathways such as IL-6, IL-1, JAK/STAT signalling, and monocyte reprogramming, future research should pursue multi-layered, precision anti-inflammatory strategies for cancer patients affected by SARS-CoV-2. Such strategies may combine selective JAK/TYK2 inhibitors with adjunctive agents targeting oxidative stress (e.g., antioxidants), NET formation and hypoxia-related signalling.

Lastly, a biomarker-driven, multimodal intervention framework should be developed to tailor therapy according to comprehensive panels integrating inflammatory cytokines (IL-6, IL-1β), viral entry factors (ACE2, TMPRSS2), immune cell ratios (neutrophil-to-lymphocyte ratio), immune exhaustion markers, and metabolic signatures. Such stratification could enable oncologists to identify high-risk patients before initiating ICI therapy, optimize therapeutic combinations and timing, and reduce irAEs while maintaining anti-tumour efficacy (Fig. 4). Integrating these multi-dimensional, biomarker-guided approaches into clinical trial design and oncology practice will be essential to advance precision immunotherapy in the evolving post-pandemic landscape.

9. Conclusion

The legacy of COVID-19 extends far beyond the acute phase of infection. Chronic inflammation, spike protein persistence and immune reprogramming are reshaping the landscape of cancer immunotherapy. A new therapeutic paradigm is emerging, one defined by precision timing, biomarker-guided personalization and the strategic integration of anti-inflammatory and viral-mimetic agents to enhance therapeutic efficacy. In this post-pandemic era, successful immunotherapy will require nuanced immune modulation rather than broad activation, aiming to maximize anti-tumour benefits while minimizing immune-related toxicity.

Authors contributions

Each author has substantially contributed to conducting the underlying research and drafting this manuscript.

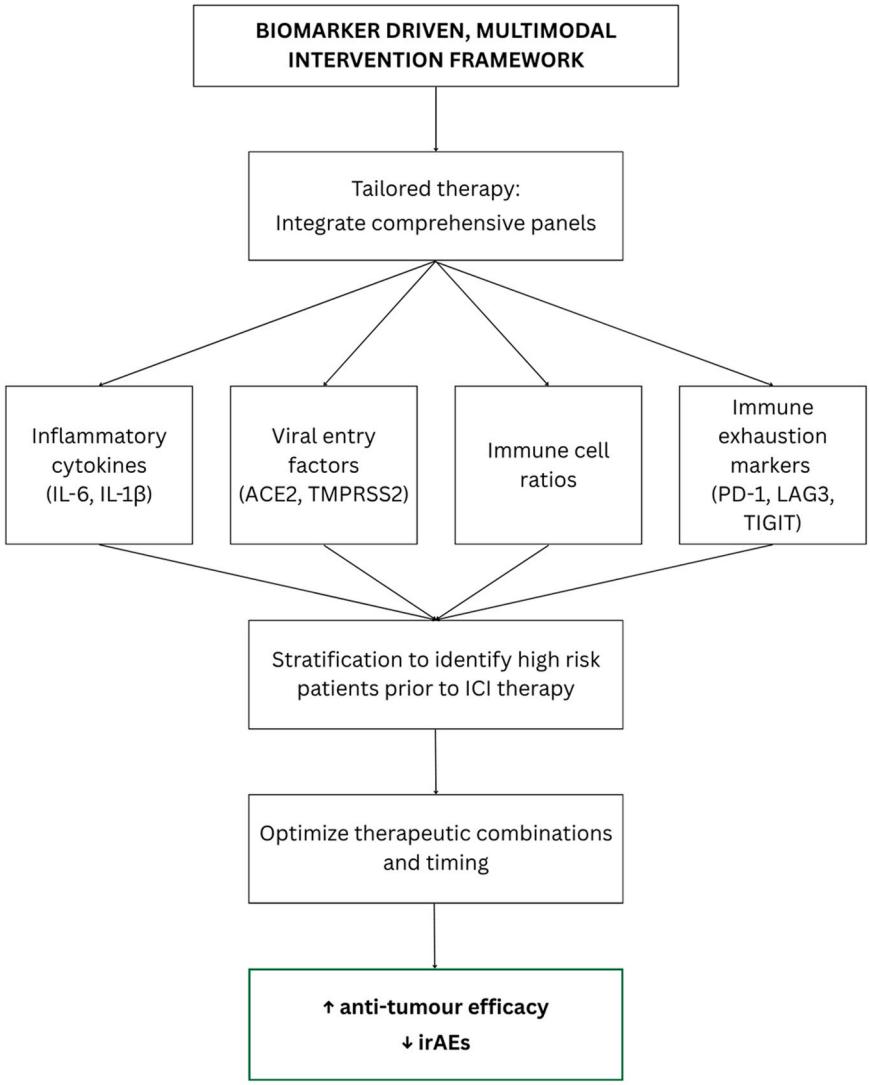

Fig. 4. Biomarker-driven, multimodal intervention framework for precision immunotherapy in the post-pandemic era.

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Declaration of Competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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