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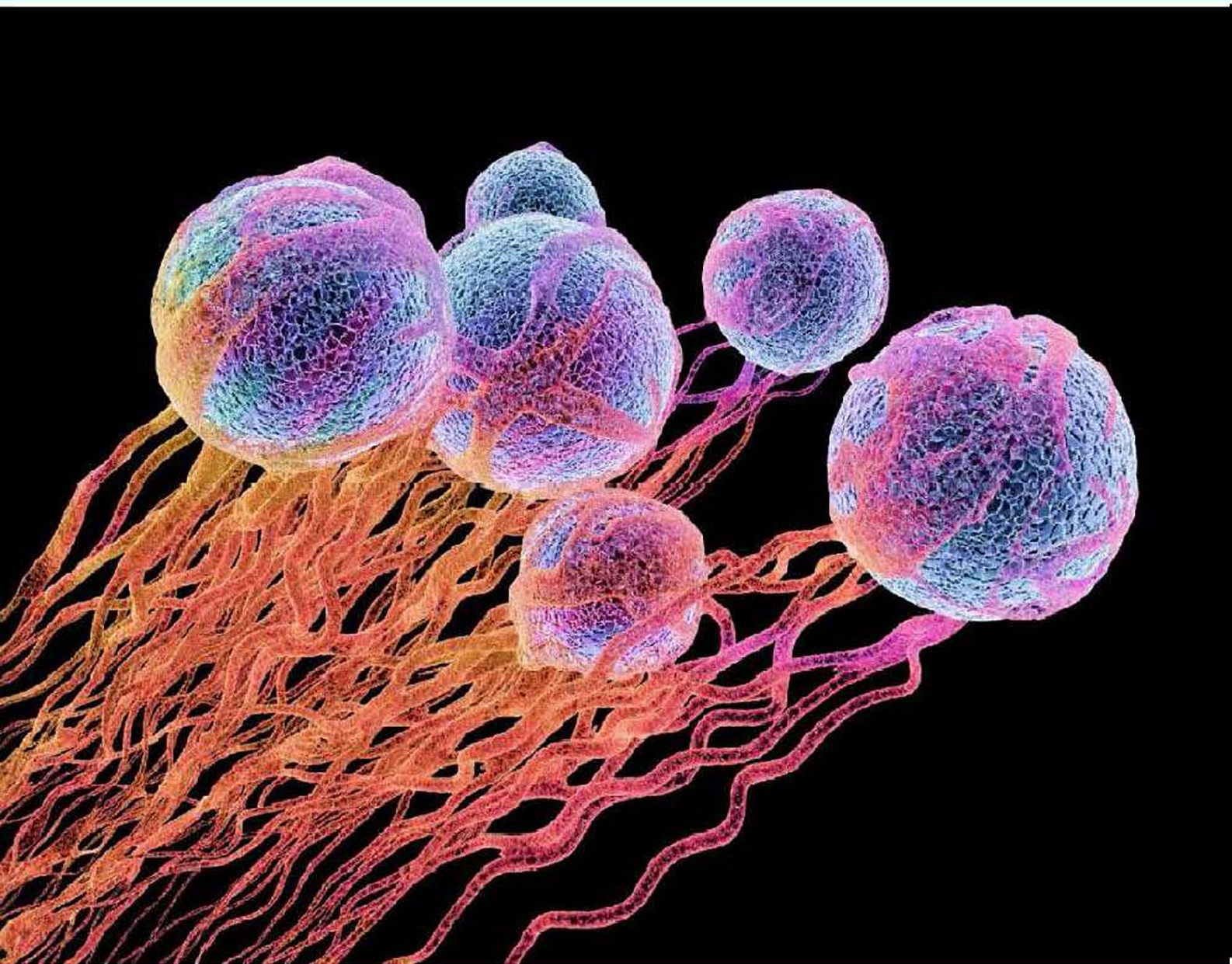

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EDITORIAL

Retrospection and prospect of *Current Cancer Reports* (CCR)

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Since the inception of *Current Cancer Reports* (CCR, ISSN: 2661-3166) in 2019, ten original Research articles, three Reviews, two Hypotheses, five Case Reports, two Correspondences and one Editorial have been published in CCR (Table 1), of which one was supported by National institutes of health (NIH) R01 fund, five supported by National Heart Lung and Blood Institute fund and had been indexed in PubMed (PMID: 31773112, PMID: 32984842, PMID: 34568835, PMID: 33898998, PMID: 33937867 and PMID: 34825193, respectively.), and one clinical trials unit is funded by the Health Research Board, UCC Cancer Trials Group in Ireland.

Table 1 Document type and quantity distribution published in CCR since 2019

Year/Vol.	Research Article	Review	Case Report	Hypothesis	Correspondence	Editorial
2022/4	2	1	1	0	1	0
2021/3	5	1	0	1	1	0
2020/2	3	0	1	2	0	0
2019/1	0	1	3	0	0	1
Total	10	3	5	3	2	1

Firstly, in view of the fact that there is no good strategy to cure cancer completely at present, the post-operative care and rehabilitation of cancer patients, the burden of patients' families and the social care measures for cancer patients have undoubtedly become the forefront and hotspot of contemporary cancer prevention and treatment research. Coughlin *et al*. shared their series of original explorations on the related topics in these respects [1–6]. Mori *et al*. explored the interactions between HIF and COX-2 with chemotherapeutic agents under normoxia and hypoxia with breast cancer cell MDA-MB-231 and SUM-149 as *in vitro* cell models under the background of 5-FU treatment, tried finding the potentials of COX-2 inhibitors for enhancing the therapeutic effects of 5-FU on triple negative breast cancer (TNBC), a subgroup of breast cancer lacking the expression of estrogen and progesterone receptors as well as HER2 [7]. Zeng *et al*. attempted the potentials of Pinus *massoniana* bark extract (PMBE), a Chinese natural product, on fighting against cancer *via* inducing the senescence of human hepatoma HepG2 cells *in vitro* [8]. Mukuku's team reported their series of research results on malignant tumors of Congo local characteristics [9–12]. Langer *et al*. displayed their critical thinking about hematogone hyperplasia [13] and novel careful observation on Day 21 serum FLC level variation during therapy of symptomatic multiple myeloma [14]. These findings suggest that the current anti-cancer research is no longer limited to the exploration of the molecular mechanism of carcinogenesis, western medicine surgery, radiotherapy and chemotherapy. The possible mechanism of Chinese medicine adjuvant treatment, as well as post-treatment nursing support and care measures have gradually become the forefronts of cancer-related research.

Secondly, two hypotheses are the other highlight of the short history of CCR. Pitkänen *et al*. boldly put forward the theory of DNA bioelectric field and think it a potential futuristic marker of cancer, ageing and death [15]. On the basis of primary experiment results and Darwinian Cancer Drug Program [16], Zhang *et al.* assumed boldly that PMBE may be used as adaptive therapy for cancer in the future [17]. These

ambitious assumptions based on mathematical calculation and experimental basis will lay the foundation for future breakthroughs in cancer detection and treatment, which should continue to be encouraged and supported.

Thirdly, statistics of source and quantity of manuscripts accepted and published in CCR through double-blind review are summarized in Figure 1 and author statistics in Figure 2.

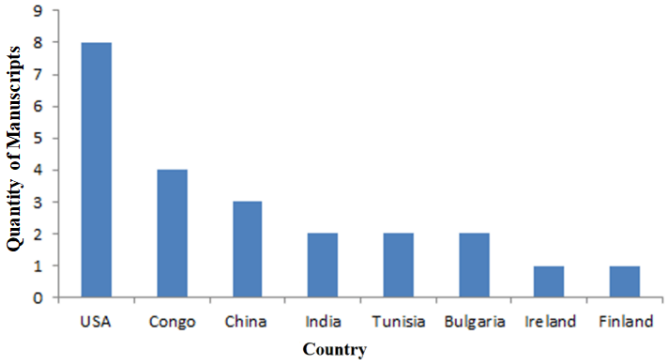

Figure 1 Statistics of country and quantity of manuscripts published in CCR since 2019

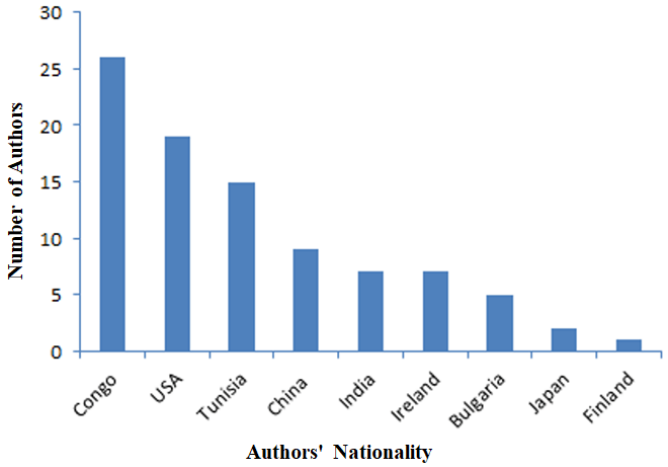

Figure 2 Statistics of authors' nationality and number of authors of manuscripts published in CCR since 2019

Obviously, Figure 1 shows that the source of manuscripts covers developed, developing and underdeveloped countries from different continents except Australia. While Figure 2 indicates that CCR paves a selective new avenue to publishing research documents performed in developing and underdeveloped countries by local scientists and researchers, and this has also been the original intention and one dream of CCR. Of note, scientists and researchers from Johns Hopkins University School of Medicine and Medical College of Georgia, Augusta University in the United States, the most developed country nowadays on the earth, have played a very good leading role in CCR growth. On behalf of the CCR editorial board, I would like to take this opportunity to express my sincere gratitude to them for their attention and support to CCR.

Taken together, CCR has published cancer-related research results of 91 scientists from 9 countries around the world to date. According to the ISI impact factor (IF) calculation formula, the current mock IF of CCR is approximately equal to 1.20.

From this year on, CCR plans to develop monographs, special issues, book review and/or abstracts of conference papers on cancer. As an old saying goes: More hands produce a stronger flame, CCR warmly welcome scientists, researchers, clinicians, clinical nursing staff and drug research and development (R&D) personnel who are engaged in cancer research and treatment all over the world to come together, hand in hand, and actively contribute, share and communicate your wisdom and exciting experimental results with global peers on our CCR platform.

Let's join hands together with CCR to help tame and docile cancer.

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EDITORIAL

Tumor microenvironment

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The tumor microenvironment (TME) has been a concept for many years, since 1889 with the presentation of Paget's "seed and soil" theory. Today, TME is now widely recognized as a hallmark of cancer, playing a critical role in cancer development. Traditionally, TME has been defined as the location where tumor cells survive within the organismal ecosystem. The classical theory indicates that oncogenes drive tumorigenesis, subsequently recruit and adapt surrounding non-malignant cells via diverse communicators like chemokines, cytokines, and vesicles [1]. However, the modern view of TME encompasses not only tumorous and nonmalignant cells but also intercellular components, intratumor microbiota, nerves, and metabolites surrounding the tumor lesion [2]. The updated TME landscape consists of six layers: tumor cell to tumor-cell environment, niche, confined tumor environment (TE), proximal TE, peripheral TE, and distal TE.

Within the TME, stromal cells such as fibroblasts, endothelial cells, and pericytes are the most abundant nonmalignant cells. Cancer-associated fibroblasts (CAFs) are the major nonmalignant stromal cells in the TME and exert diverse and prominent tumor-supporting effects. Physically, CAFs promote matrix adhesion and mesenchymal morphology that result in increased stiffness and collagen fiber alignment. This leads to increased secretion of type I collagen by CAFs, supporting tumor invasion and migration. Subsequently, CAFs release diverse matrix metalloproteinases (MMPs) to degrade and remodel the extracellular matrix (ECM), which contributes to the stimulation of stemness and epithelial-mesenchymal transition. CAFs secrete the primary chemokine, C-X-C motif ligand 12 (CXCL12), which promotes T cell retention by binding to its receptor atypical chemokine receptor 3 (ACKR3) on the surface of T cells [3]. However, CXCL12 also recruits C-X-C motif chemokine receptor 4 $(CXCR4)^+$ myeloid cells to form an immunosuppressive microenvironment [4]. Metabolically, CAFs exhibit a phenomenon called "metabolic symbiosis" where they consume glucose and produce lactate, which cancer cells prefer utilizing via monocarboxylate transporter 1 (MCT1) transporters [5]. Immunologically, CAFs orchestrate a particular structural tissue organization through dense and aligned fiber deposition to exclude T cells from tumor nests [6]. Additionally, leucine-rich-repeat-containing protein 15 $(LRRC15)^+$ CAFs directly suppress the effector function of tumour-infiltrating cluster of differentiation 8 $(CD8)^+$ T cells and restrict the efficacy of checkpoint blockade [7]. Further studies are necessary to better understand the complicated roles of endothelial cells and pericytes in cancer progression [8, 9].

The TME comprises a diverse population of immune cells, including myeloid-derived suppressor cells (MDSC), neutrophils, dendritic cells (DC), innate lymphoid cells (ILC), natural killer cells (NK), lymphocytes, and macrophages [10, 11]. Within the TME, cytokines manipulate immune function, leading to weakened immune responses that promote tumor progression [12]. $CD8^+$ T cells represent the primary adaptive immune cells in cancer and selectively recognize and eradicate tumor cells expressing tumor-specific antigens, including tumor-specific neoantigens and self-antigens [13]. However, over the course of tumorigenesis, tumor-reactive $CD8^+$ T cells become dysfunctional. Various immunosuppressive elements within the TME, such as forkhead box protein P3 $(FOXP3)^+$ and cluster of differentiation 4 $(CD4)^+$ regulatory T cells, MDSCs, tumor-associated macrophages (TAMs), interleukin-10 (IL-10), inhibitory checkpoints, and metabolic changes such as hypoxia or indoleamine

2,3-dioxygenase, contribute to this dysfunction [14, 15]. Overcoming the immunosuppressive TME and improving the functionality of $CD8^+$ T cells can enhance responses to therapeutic reprogramming.

Recent advancements in cancer biology have identified microbiota as an important component of the tumor microenvironment, specifically categorized as 'intratumor microbiota' [16]. Numerous studies have extensively supported the presence of intratumor microbiota, and their abundance is found to be tumor-specific. The enrichment of microbiota has been discovered in breast, bone, and pancreatic cancers, but not in cancer tissues exposed to external environment [17]. As few studies have specifically interrogated its original source, its origin remains a mystery. Intratumor bacteria have several similar characteristics, including lower diversity and abundance of the microbial community in cancer tissues [18]. Commensal organisms tend to survive in the intracellular space. Functionally, intratumor microbiota can modulate cancer cell-intrinsic and cell-extrinsic properties. Intratumor microbiota can induce a migratory and invasive phenotype, initiate stemness, and resist lethal stimuli [19]. Intratumor bacteria are also important regulators that can create a tumor-supporting microenvironment through the production of specific metabolites and immune modulation [20, 21]. This discovery provides a unique perspective to understand networks of the cancer ecosystem and reshapes the current conceptual framework of the TME.

The innervated microenvironment (IME) is a specialized micro-ecosystem that forms through communication between nerves and cancer cells via nerve-derived neurotransmitters or neuropeptides [22]. IMEs are categorized as intracranial or extracranial innervated niches. In the intracranial IME, active neurons promote the gliomas growth through the neuroligin-3 (NLGN3)-activated PI3K/mTOR pathway [23]. Perineural invasion (PNI) refers to cancer invasion in or around nerves, which is associated with poor cancer prognosis. Peripheral nerves, including sympathetic, parasympathetic, and sensory nerves, are present in the IME and make physical contact with cancer parenchyma or nearby nerves. The secretion of neuropeptides or neurotransmitters like catecholamine, acetylcholine and dopamine plays a crucial role in neuromodulation within the IME [24]. Additionally, Schwann cells from nerves facilitate cancer invasion. When activated by cancer cells, Schwann cells collectively function as tumor-activated Schwann cell tracks (TAST), promoting cancer cell migration and invasion [25]. TAST exhibit elevated HIPPO-transcriptional co-activator with PDZ-binding motif (TAZ)/yes-associated protein (YAP) expression, and hyperactivity of TAZ/YAP in Schwann cells activates oncogenic programs, including platelet-derived growth factor receptor (PDGFR) signaling, leading to high-grade nerve-associated tumors [26]. Recent studies have demonstrated a tumor-nerve-immunity cycle in TME that mediates communication among cancer cells, immune microenvironment, and innervation. The Hypothalamic-pituitary (HP) unit is able to expedite myelopoiesis and immunosuppression to promote tumor growth through the production of α-melanocyte-stimulating hormone (α-MSH). α-MSH combines to melanocortin receptor melanocortin 5 receptor (MC5R) to promote myeloid cell recruiting, immunosuppression, and tumor growth [27].

Various innovative approaches are available to gain detailed insights into the immunological features of tumors. For instance, single-cell and spatial multi-omics techniques provide a comprehensive understanding of TME [28]. Additionally, immunomics, based on next-generation sequencing (NGS) technologies and mass-spectrometric techniques, offers novel insights into tumor immunology. In recent years, strategies targeting the TME have gained significant attention due to its critical role in tumor progression and cancer treatment efficacy. These approaches primarily focus on cancer immunotherapy, such as vaccines, immune checkpoint blockade (ICB), adoptive immune cell therapy, as well as targeting tumor angiogenesis, ECM, and CAFs [29]. Despite inducing durable remissions in some patients and cancer types, these strategies fail to achieve long-term responses for most patients. However, continued advances in technology and therapy have the potential to integrate basic microenvironmental insights with clinical observations to benefit all cancer patients through TME-targeting therapies.

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RESEARCH ARTICLE

Risk of severe immune-related adverse events in cancer patients with pre-existing autoimmunity receiving immune checkpoint inhibitor therapy

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Abstract: Purpose: To evaluate the frequency and severity of irAEs in patients with pre-existing autoimmunity, including irAE-related morbidity and mortality, irAE-related management and resolution, and outcome of ICI rechallenge, to better understand the treatment options for this vulnerable patient population. **Methods**: We designed a retrospective, single-center, case-control study at a large, academic medical center to evaluate the incidence and severity of irAEs in patients with pre-existing autoimmunity compared to controls. Controls were matched 2:1 for age, sex, cancer histology, and ICI class. Patients were identified with ICD 9 and 10 codes followed by manual chart extraction. Cases were defined as patients with pre-existing, systemic autoimmunity. The primary outcome was severe irAE (Grade 3 or higher by Common Terminology Criteria for Adverse Events) within 6 months of ICI therapy. Secondary outcomes included response to ICIs, resolution of the irAE, ICI rechallenge success, and survival. Statistical analyses were performed by Chi-square, Fishers exact, Mann-Whitney, and Log-rank tests. **Results**: Of 3,130 patients treated with ICIs from 2015-2021, 28 cases with pre-existing autoimmune disease were identified and were matched with 56 controls. Pre-existing autoimmune conditions included antiphospholipid syndrome, inflammatory polyarthritis, juvenile rheumatoid arthritis, multiple sclerosis, psoriatic arthritis, rheumatoid arthritis, and type I diabetes. Multiple cancer histologies, including genitourinary, gynecologic, head & neck, hepatobiliary, lung, melanoma, and pancreatic, were represented. Six of 28 cases (21.4%) experienced severe irAEs compared to 9/56 (16.1%) controls; the odds of developing a severe irAE were not significantly different (OR 0.43, 95% CI 0.083-2.33, $p = 0.627$, ns). Moreover, there were no significant differences in overall survival or tumor response between the two groups. The majority of irAEs resolved without long-term sequelae (66.7% of cases, 55.6% of controls). The majority of patients who were rechallenged with ICIs were successful in continuing therapy (66.7% of cases, 100% of controls). **Conclusion**: Our study suggests that patients with pre-existing autoimmune disease can be treated with ICI cancer therapies and experience rates of severe irAEs and overall survival that are similar to those of the general population. These data can aid oncologists in discussing risks and benefits of ICIs when treating patients with pre-existing autoimmunity and solid tumors.

Keywords: immune checkpoint inhibitor, autoimmunity, immune related adverse events, cancer

Abbreviations

ICI:	immune checkpoint inhibitor
irAE:	immune related adverse event
PD1:	programmed death protein 1
PD-L1:	programmed death ligand 1
CTLA-4:	cytotoxic T lymphocyte antigen 4
CTCAE:	Common Terminology Criteria for Adverse Event
ICD:	International Classification of Diseases
ECOG:	Eastern Cooperative Oncology Group
RECIST:	Response Evaluation Criteria in Solid Tumors
PD:	progression of disease
SD:	stable disease

PR: partial response
CR: complete response
IQR: interquartile range
SD: standard deviation

1 Introduction

Immune checkpoint inhibitors (ICIs) are a type of cancer immunotherapy used to treat an expanding group of solid and hematologic malignancies. These agents block regulatory molecules on T cells, such as cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death protein-1 (PD-1)/programmed death ligand-1 (PD-L1), thereby increasing immune activation and anti-tumor immune responses [1]. These agents have revolutionized the field of oncology since the initial approval of ipilimumab in 2011, and now include multiple single agent and combination regimens, including atezolizumab, avelumab, cemiplimab, dostarlimab, durvalumab, nivolumab, pembrolizumab, relatlimab, and tremelimumab [1, 2].

The most serious adverse effect from ICI therapy is autoimmune destruction of healthy tissues, termed immune-related Adverse Events (irAEs). The incidence of irAEs varies depending on ICI regimen with a wide range reported in the literature, between 10-80% [3, 4]. In general, irAEs occur more frequently with anti-CTLA-4 monotherapy compared with anti-PD-1/PD-L1 monotherapy, 72% and 66%, respectively [5–7]. Combination ICI therapy leads to even higher rates of irAEs, with reported rates over 90% [8]. IrAEs can affect nearly any tissue in the body, including the skin, gut, liver, endocrine organs, lungs, joints, nervous system, kidney, eye, heart, and blood [7]. The NIH Common Terminology Criteria for Adverse Events (CTCAEs) grade irAEs from 1-5, with Grade 1 as the least severe and Grade 5 as resulting in death [9, 10]. Grade 3 or higher irAEs signify severe symptoms requiring hospitalization and/or other emergent measures, and have been reported in 2.5-18% of patients [3]. The most fatal irAEs reported in the literature are colitis, hepatitis, neurotoxicity, and myocarditis [7].

Administering ICIs to patients with pre-existing autoimmune disease presents a dilemma for oncologists. Not treating a potentially fatal disease like cancer due to the fear of toxicity in these patients has been very unsettling. These patients have historically been excluded from clinical trials of ICI therapy due to concerns of inducing severe irAEs in patients whose immune systems are already overactive, including potential flares of underlying autoimmune disease. As a result, little is known about the safety and efficacy of ICIs in this population [11]. Several retrospective studies have sought to evaluate the risk of irAEs and exacerbation of autoimmune disease in patients with pre-existing autoimmunity by evaluation of this subgroup within larger cohorts. A systematic review by Abdel-Wahab et al. identified 123 cases with pre-existing autoimmunity from 49 retrospective studies, including case reports, case series, and observational studies. This report found that 92/123 patients (75%) experienced an autoimmune exacerbation and/or de-novo irAE, which resulted in 21 patients (17.1%) permanently discontinuing ICI therapy and 5 patient deaths (4.1%) [12]. On the other hand, more than half of the irAEs in patients with pre-existing autoimmunity resolved and did not require discontinuing ICI therapy [12]. In another review of the topic, Tison and colleagues evaluated 24 studies of patients receiving ICIs, with a focus on patients with pre-existing rheumatologic diseases [2]. They reported that 6-83% of study participants experienced flares of their autoimmune disease and that 16-90% of patients experienced irAEs involving other organs, although fewer than 35% of patients experienced severe (Grade $\geq$ 3) irAEs [2]. Similarly, another literature review by Wu et al. reinforced the notion that irAEs in patients with pre-existing autoimmunity are manageable [13].

These studies were limited by the use of International Classification of Diseases (ICD) codes for the identification of pre-existing autoimmunity, inclusion of autoimmune diseases with only limited systemic manifestations (such as vitiligo and Hashimoto's thyroiditis), and the absence of matched control groups for comparison [2, 12, 13]. Given the increasing recognition of irAEs in clinical practice, more indications for ICI use as cancer therapy, varying irAE incidence across regimens, and evolving approaches to treatment of irAEs, a control group is crucial to accurately evaluate the frequency of irAEs in this vulnerable population. Placais et al. recently published a case-control study of patients with autoimmune disease and melanoma, but excluded other cancer histologies [14]. Similarly, we previously studied the use of ICIs in patients with autoimmune diseases and genitourinary cancers in addition to patients with pre-existing type 1 diabetes mellitus [15, 16]. However, given the limited data, there remains clinical uncertainty about the safety of ICI therapy in patients with pre-existing systemic autoimmunity.

The purpose of this study was to evaluate the frequency and severity of irAEs in patients with pre-existing autoimmunity, including irAE-related morbidity and mortality, irAE-related

management and resolution, and outcome of ICI rechallenge, to better understand the treatment options for this vulnerable patient population.

2 Methods

2.1 Study Design & Patient Selection

This is a retrospective nested case-control study conducted at a single academic center. Our patient population encompassed 3,130 adult patients (age $\geq$ 18 years) who received one or more FDA-approved ICIs for treatment of a solid malignancy from 2015-2021 within this health system.

Cases and controls were stratified by the presence or absence of a pre-existing autoimmune condition. Cases were defined as patients with pre-existing autoimmunity with one of the following conditions: antiphospholipid syndrome (ICD 9 714; ICD 10 M05, M06.9), chronic inflammatory demyelinating polyneuropathy (ICD 9 357.81; ICD 10 G61.81), dermatomyositis (ICD 9 710.3; ICD 10 M33), diffuse connective tissue disease (ICD 9 710.9, ICD 10 M35.9), inflammatory polyarthritis (ICD 9 714.9; ICD 10 M06.4), juvenile arthritis (ICD 9 714.3; ICD 10 M08), multiple sclerosis (ICD 9 340; ICD 10 G35), psoriatic arthritis (ICD 9 696; ICD 10 L40), rheumatoid arthritis (ICD 9 714; ICD 10 M05, M06.9), systemic lupus erythematosus (ICD 9 710; ICD 10 M32), systemic sclerosis (ICD 9 710.0; ICD 10 M34), or type I diabetes (ICD 9 250.03 and 205.010; ICD 10 E10.9, E10.65) [17]. Controls were patients without any of the aforementioned autoimmune conditions and were selected in a 2:1 ratio to cases. Controls were matched for sex, age, organ of tumor origin, and ICI class (anti-PD1 or PDL1 monotherapy, or combination anti-CTLA4 with anti-PD1 or PDL1). Patients who were pregnant or had a history of stem cell and/or solid organ transplant were excluded.

2.2 Data Collection

Cases were first ascertained using ICD 9 and 10 codes for the autoimmune diseases listed above. The autoimmune diagnosis was confirmed via manual chart review of the electronic medical record. Data including age at cancer diagnosis, gender, Eastern Cooperative Oncology Group (ECOG) performance status prior to immunotherapy, cancer diagnosis, cancer staging, and ICI type(s) were obtained by manual chart review [18]. The primary outcome was the development of severe irAEs within six months of ICI exposure, with severe defined as Grade 3 or higher by CTCAE criteria [10]. Secondary outcomes included response to ICI, resolution of the irAE, ICI rechallenge success, and survival.

2.3 Statistical Analyses

Statistical analyses were performed using Prism software (v9.4, GraphPad Software, Boston, Massachusetts USA, www.graphpad.com). Baseline characteristics were reported with descriptive statistics. Mann-Whitney testing was used for comparisons between non-parametric variables. Chi-square or Fisher's exact test was used to compare differences between proportions and categorical variables, and odds ratios (OR) were determined using the Baptista-Pike method. Conditions for performing Chi-square calculations were not met in all subgroup analyses; therefore, qualitative analysis was performed for age, gender, ECOG score, and baseline disease burden (metastatic or non-metastatic on presentation). Survival was compared between cases and controls by Log-Rank testing. Significance for all statistical tests was defined as alpha = 0.05, with correction for multiple comparisons.

3 Results

3.1 Patient Characteristics

Of 3,130 adult cancer patients who received treatment with an FDA-approved ICI within the UCLA Health system between 2015 and 2021, we identified 28 cases with pre-existing systemic, chronic autoimmune disease: 1/28 (3.6%) with antiphospholipid syndrome, 3/28 (10.7%) with inflammatory polyarthritis, 1/28 (3.6%) with juvenile rheumatoid arthritis, 3/28 (10.7%) with multiple sclerosis, 3/28 (10.7%) with psoriatic arthritis, 14/28 (50.0%) with rheumatoid arthritis, and 3/28 (10.7%) with type I diabetes mellitus (Table 1). Controls matched for sex, age within 10 years, ICI regimen, and cancer type were selected in a 2:1 ratio with cases (Table 1).

The median age at cancer diagnosis of the cases was 65.5 years (IQR 60.3-74.8) and the

Table 1 Baseline characteristics of cases and controls

Clinical Parameter	Cases (28) n (%)	Controls (56) n (%)	*p*-Value
Age (years)			
20-29	2 (7.1%)	1 (1.8%)	
30-39	0 (0.0%)	3 (5.4%)	
40-49	0 (0.0%)	3 (5.4%)	
50-59	4 (14.3%)	7 (12.5%)	
60-69	12 (42.9%)	18 (32.1%)	
70-79	7 (25.0%)	16 (28.6%)	
80-89	2 (7.1%)	7 (12.5%)	
90-99	1 (3.6%)	1 (1.8%)	> 0.999
Sex			
Female	13 (46.4%)	26 (46.4%)	
Male	15 (53.6%)	30 (53.6%)	> 0.999
ECOG			
0	9 (32.1%)	22 (39.3%)	
1	12 (42.9%)	28 (50.0%)	
2	2 (7.1%)	2 (3.6%)	
3	2 (7.1%)	1 (1.8%)	
N/A	3 (10.7%)	3 (5.4%)	0.202
Metastatic Disease			
Y	22 (78.6%)	50 (89.3%)	
N	6 (21.4%)	6 (10.7%)	0.202
Cancer Type			
Genitourinary	8 (28.6%)	16 (28.6%)	
Gynecologic	3 (10.7%)	6 (10.7%)	
Head & Neck	1 (3.6%)	2 (3.6%)	
Hepatobiliary	3 (10.7%)	6 (10.7%)	
Lung	7 (25.0%)	14 (25.0%)	
Melanoma	4 (14.3%)	8 (14.3%)	
Ovarian	1 (3.6%)	2 (3.6%)	
Pancreatic	1 (3.6%)	2 (3.6%)	> 0.99
ICI Regimen			
CTLA-4	0 (0.0%)	0 (0.0%)	
PD-1	22 (78.6%)	33 (58.9%)	
PD-L1	1 (3.6%)	11 (19.6%)	
CTLA-4 + PD-1	5 (17.9%)	11 (19.6%)	
CTLA-4 + PD-L1	0 (0.0%)	0 (0.0%)	
PD-1 + PD-L1	0 (0.0%)	1 (1.8%)	0.10

Note: ECOG: Eastern Cooperative Oncology Group; ICI: Immune checkpoint inhibitor; CTLA-4: Cytotoxic T lymphocyte antigen; PD-1: Programmed death protein; PD-L1: Programmed death ligand

median age at cancer diagnosis of the controls was 65.0 years (IQR 59.3-73.8). Thirteen of the 28 cases (46.4%) were female, and 26/56 controls were female (46.4%). The majority of cases (21/28, 75.0%) had an ECOG score of 0-1 prior to treatment with ICIs, 4/28 (14.2%) had an ECOG score of 2 or higher, and 3/28 (10.7%) had an ECOG score that was not reported in the medical record. In the control group, 50/56 (89.3%) had an ECOG score of 0-1, and 3/56 (5.4%) had an ECOG score of 2 or higher. Three of 56 (5.4%) controls had an ECOG score that was not reported in the medical record. Most patients with pre-existing autoimmune disease who were treated with ICI therapy had metastatic disease [22/28 (78.6%)], as did the controls (Table 1).

The histologic types of cancers in our cases included 8/28 (28.6%) genitourinary, 4/28 (14.3%) gynecologic, 1/28 (3.6%) head and neck, 3/28 (10.7%) hepatobiliary, 7/28 (25.0%) lung, 4/28 (14.3%) melanoma, and 1/28 (3.6%) pancreatic. In controls, 16/56 (28.6%) had genitourinary malignancies, 8/56 (14.3%) gynecologic 2/56 (3.6%) head & neck, 6/56 (10.7%) hepatobiliary, 14/56 (25.0%) lung, 8/56 (14.3%) melanoma, and 2/56 (3.6%) pancreatic. Most cases received PD-1 or PD-L1 monotherapy [23/28 (82.1%)], while 5/28 (17.9%) received combination therapy of CTLA-4 and PD-1 inhibitors. Similarly, 44/56 (78.6%) of controls received PD-1 or PD-L1 monotherapy and 11/56 (19.6%) received combination therapy of CTLA-4 and PD-1 inhibitors, while 1 (1.8%) received PD1 and PDL1 inhibitors (Table 1).

3.2 IRAE Incidence and Outcomes

The incidence of all-grade irAEs in the total population encompassing cases and controls was 37/84 (44.0%).

3.2.1 All Cases

Four of 28 (14.2%) cases experienced Grade 1-2 irAEs, of whom 3 (3/28, 10.7%) had received PD-1 or PD-L1 monotherapy and 1 (1/28, 3.6%) had received combination therapy. These irAEs included maculopapular rash (n = 1), arthralgias (n=1), adrenal insufficiency (n = 1), and myositis (n = 1). Only one of these irAEs was an autoimmune disease flare; a patient with a history of rheumatoid arthritis experienced Grade 1 arthritis after 1 cycle of nivolumab. Six of 28 (21.4%) cases experienced Grade $\geq$ 3 irAEs, of whom 3 (3/28, 10.7%) had received PD-1 or PD-L1 monotherapy and 3 (3/28, 10.7%) received combination therapy. These irAEs included hyperglycemia (n = 1), bullous dermatitis (n = 1), colitis (n = 1), transaminitis (n = 2), and arthritis (n = 1) (Table 2, Figure 1). Only one of these irAEs was an autoimmune disease flare (case #5); this patient had a history of juvenile rheumatoid arthritis and received 9 cycles of nivolumab (Table 2). The other irAEs involved tissues unrelated to patients' autoimmune diseases.

Table 2 Summary of Grade 3 & 4 irAEs and their outcomes reported in case subjects with pre-existing autoimmune disease

Case	Sex	Age at Cancer Diagnosis	Pre-Existing Autoimmune Disease	Status of Autoimmune Condition	Cancer	Metastatic Disease prior to ICI Therapy	ICI Line of Therapy	Mono vs. Dual ICI Therapy	ICI(s)
1	F	54	Multiple Sclerosis	Controlled off medications	Endometrial	Yes	Third	Mono	Pembrolizumab (46 cycles)
2	M	64	Multiple Sclerosis	Controlled on glatiramer acetate	Renal	Yes	Third	Dual	Ipilimumab (2 cycles), Nivolumab (6 cycles)
3	M	61	Rheumatoid Arthritis	Controlled on methotrexate	Melanoma	Yes	First	Dual	Ipilimumab (4 cycles), Nivolumab (22 cycles)
4	F	54	Rheumatoid Arthritis	Controlled off medications	Melanoma	Yes	First	Dual	Ipilimumab (4 cycles), Nivolumab (4 cycles)
5	M	69	Polyarthritis	Controlled off medications	Urothelial	Yes	Second	Mono	Nivolumab (31 cycles)
6	F	21	Juvenile Rheumatoid Arthritis	Controlled off medications	Ovarian	No	Second	Mono	Nivolumab (9 cycles)

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Treatment Response	irAE Type	irAE Grade	irAE Treatment	Rechallenged	Immunotherapy Cessation	irAE Long-Term Outcome	Follow-Up Time in Months since irAE
Stable	Hyperglycemia	3	Insulin	No	Yes	Insulin-Dependent Diabtes Mellitus	6
Progressive	Bullous Dermatitis	3	Steroids, Rituixmab	No	Yes	Resolved	7
Progressive	Diarrhea	5	Supportive Measures	No	Yes	Death	N/A
Partial	Transaminitis	4	Steroids	Yes	Yes	Resolved	15
Progressive	Transaminitis	3	Steroids	Yes	No	Resolved	33
Partial	Arthritis	3	Steroids, Methotrexate, Sulfasalazine, Leflunomide	Yes	No	Resolved	88

Note: irAEs: immune related adverse events; ICI: immune checkpoint inhibitor

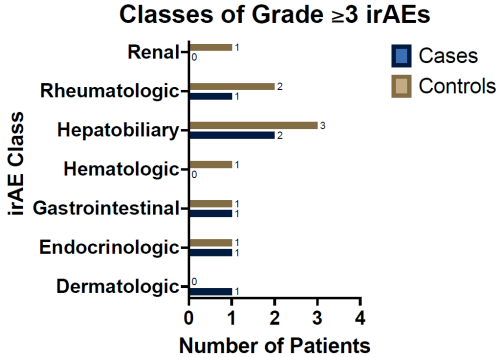

Figure 1 Among patients with severe irAEs, the most common classes of irAEs were hepatobiliary (n = 5) and rheumatologic (n = 3).

3.2.2 All Controls

Eighteen of 56 (32.1%) controls experienced Grade 1-2 irAEs, of whom 14 (14/56, 25%) had received PD-1 or PD-L1 monotherapy and 4 (4/56, 7.1%) had received combination therapy. IrAEs included hypothyroidism (n = 7), pneumonitis (n = 3), maculopapular rash (n = 3), bullous dermatitis (n = 2), hyperbilirubinemia (n=1), arthritis (n = 1), and pruritus (n = 1). Nine of 56 (16.1%) controls experienced Grade $\geq$ 3 irAEs, of whom 6 (6/56, 10.7%) had PD-1 or PD-L1 monotherapy and 3 (3/56, 5.4%) received combination therapy. These irAEs included hyponatremia (n = 1), nephritis (n = 1), arthritis (n = 2), hepatitis (n = 3), colitis (n = 1), and anemia (n = 1) (Table 3, Figure 1). Three controls had pre-existing autoimmune conditions that were not included in our search, including hypothyroidism (n = 2) and immune thrombocytopenic purpura (n = 1); none of these patients developed Grade $\geq$ 3 irAEs.

Table 3 Summary of Grade 3 & 4 irAEs and their outcomes reported in control subjects

Control	Sex	Age at Cancer Diagnosis	Cancer	Metastatic Disease prior to ICI Therapy	ICI Line of Therapy	Mono vs. Dual ICI Therapy	ICI(s)	Treatment Response	irAE Type
1	F	67	Lung	Yes	Second	Mono	Pembrolizumab (1 cycle)	Stable	Hyponatremia
2	F	62	Urothelial	Yes	Second	Mono	Durvalumab (3 cycles)	Progressive	Nephritis
3	F	61	Urothelial	Yes	First	Dual	Ipilimumab (3 cycles), Nivolumab (3 cycles)	Complete	Arhritis
4	F	60	Cervical	Yes	Third	Mono	Pembrolizumab (9 cycles)	Stable	Arhritis
5	F	26	Cervical	Yes	Third	Mono	Nivolumab (1 cycle)	Progressive	Hepatitis
6	F	32	Cervical	Yes	Second	Mono	Pembrolizumab (7 cycles)	Progressive	Anemia
7	F	72	Hepatobiliary	Yes	> Third	Mono	Nivolumab (4 cycles)	Progressive	Hepatitis
8	M	75	Lung	Yes	Second	Dual	Nivolumab (2 cycles), Ipilimumab (2 cycles), Atezolizumab (6 cycles), Durvalumab (1 cycle)	Progressive	Hepatitis
9	M	70	Melanoma	Yes	First	Dual	Ipilimumab (2 cycles), Nivolumab (2 cycles)	Stable	Colitis

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irAE Grade	irAE Treatment	Rechallenged	Immunotherapy Cessation	irAE Long-Term Outcome	Follow-Up Time in Months since irAE
3	Supportive Measures	No	Yes	Resolved	4
3	Supportive Measures	Yes	No	Resolved	4
3	Steroids, Methotrexate	Yes	No	Arthritis on Methotrexate	46
3	Steroids	Yes	No	Arthritis on NSAIDs	40
5	Steroids	No	Yes	Death	1
4	Steroids, Transfusions	No	Yes	Transfusion- Dependent Anemia	5
3	Steroids	Yes	No	Resolved	7
3	Steroids	Yes	No	Resolved	44
3	Steroids	No	Yes	Resolved	2

Note: irAEs: immune related adverse events; ICI: immune checkpoint inhibitor

3.2.3 Comparison

4/28 (14.2%) of cases developed a low-grade (1-2) irAE compared to 18/56 (32.1%) of controls. 6/28 (21.4%) of cases developed a high-grade ($\geq$ 3) irAE compared to 9/56 (16.1%) of controls. Therefore, cases and controls demonstrated a similar odds of developing a low-grade irAE compared to a high-grade irAE [OR 0.33, 95% CI 0.091 to 1.38, p = 0.258, not significant (ns), Figure 2]. Subgroup analysis of 23 cases and 44 controls treated with anti-PD1/PD-L1 monotherapy found that 6/23 (26.0%) cases experienced all-grade irAEs and 20/44 (45.4%) controls experienced all-grade irAEs. There was no significant difference in the odds of developing a severe irAE between cases and controls (OR 0.43, 95% CI 0.083-2.33, p = 0.627, ns, Figure 3).

3.3 Cases with Severe IRAES (Grade 3-5)

3.3.1 Baseline Characteristics

Half (3/6, 50%) of cases who experienced severe irAEs were female. The median age at time of cancer diagnosis was 57.5 years (IQR 45.8-69.0). The cases' pre-existing autoimmune diseases included multiple sclerosis (n = 2) and multiple types of arthritis (n = 4) (Table 2).

Case #2 and Case #3 were both taking immunosuppressants at baseline (glatiramer acetate

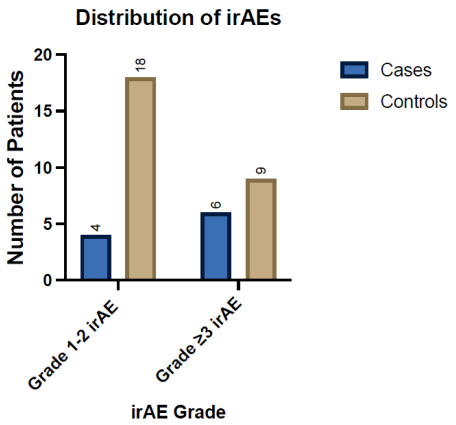

Figure 2 4/28 (14.2%) of cases developed a low-grade (1-2) irAE compared to 18/56 (32.1%) of controls. 6/28 (21.4%) of cases developed a high-grade ($\geq$ 3) irAE compared to 9/56 (16.1%) of controls. Cases and controls demonstrated a similar odds of developing a low-grade irAE compared to a high-grade irAE (OR 0.33, 95% CI 0.091 to 1.38, p = 0.258, NS).

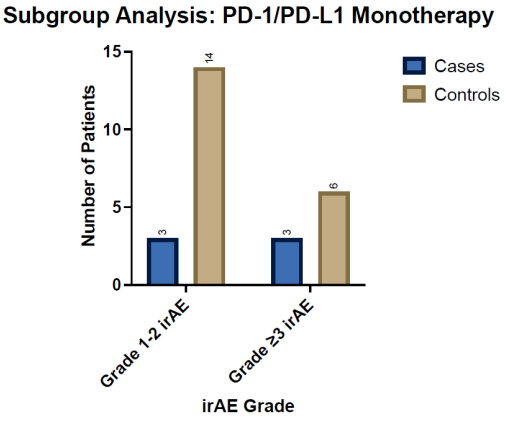

Figure 3 In an anti-PD-1/PDL-1 monotherapy subgroup analysis, the odds of developing a low-grade (1-2) irAE were not significantly different than the odds of developing a high-grade ($\geq$ 3) irAE among cases and controls (OR 0.43, 95% CI 0.083 to 2.33, p = 0.627, ns).

for multiple sclerosis and methotrexate for rheumatoid arthritis, respectively); others remained controlled off immunosuppressants (Table 2). Cancer histologies included gynecologic (n = 2), genitourinary (n = 2), and melanoma (n = 2) (Table 2). All cases except for one (Case #6) had metastatic disease prior to ICI therapy (Table 2).

3.3.2 Outcomes

We evaluated patient response to ICI therapy using Response Evaluation Criteria in Solid Tumors (RECIST) [19]. Cancer outcomes of cases who had severe irAEs included 3/6 (50.0%) with progression of disease (PD), 1/6 (16.7%) with stable disease (SD), and 2/6 (33.3%) with a partial response (PR). None of the cases had a complete response to ICIs (Table 2, Figure 4).

Two of the three (66.7%) cases with PD were taking autoimmune agents at baseline (Case #2 and Case #3, Table 2). Case #2 was taking glatiramer acetate for multiple sclerosis and had progression of his renal cell carcinoma after two cycles of ipilimumab and six cycles of nivolumab. Case #3 was taking methotrexate for rheumatoid arthritis and had progression of his melanoma after 4 cycles of ipilimumab and 22 cycles of nivolumab. Case #3 then experienced Grade 5 diarrhea, thought to be ICI colitis from combination therapy superimposed on the patient's history of microscopic colitis. Upon further chart review, the patient declined to take antidiarrheal agents and preferred not to present to the hospital for intravenous hydration, so this death may have been preventable under different circumstances.

Only 1 case developed a long term irAE; Case #1 developed insulin-dependent diabetes

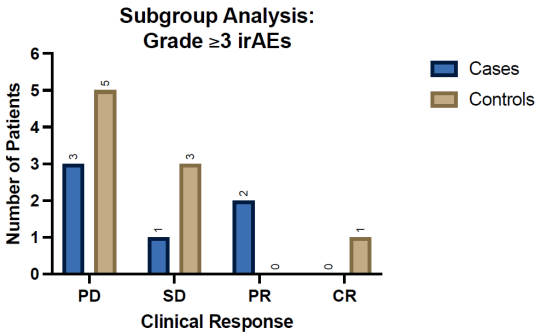

Figure 4 In patients who experienced Grade $\geq$ 3 irAEs, the odds of developing progressive disease versus developing stable disease or a positive clinical response were not significantly different among cases and controls (OR 0.80, 95% CI 0.13-5.10, p = 0.999, ns). PD: Progressive Disease; SD: Stable Disease; PR: Partial Response; CR: Complete Response.

mellitus after experiencing irAE hyperglycemia. This patient had a history of multiple sclerosis controlled off medications and received 46 cycles of pembrolizumab for endometrial cancer. The remaining 4/6 (66.7%) cases, excluding Case #3 who died, did not experience long-term sequelae of the irAEs. Their irAEs resolved with supportive measures and/or immunosuppressants.

Overall, 5/6 (83.3%) cases with Grade $\geq$ 3 irAEs survived. Moreover, 2/3 (66.7%) cases (Case #5 and Case #6) were successfully rechallenged with ICIs without further irAEs. Case #5 had a history of polyarthritis, recovered from nivolumab-induced transaminitis, and was able to continue nivolumab for her urothelial cell carcinoma. Similarly, case #6 had a history of juvenile rheumatoid arthritis, recovered from nivolumab-induced Grade 3 arthralgias, and was able to continue nivolumab for ovarian cancer. Case #4 had a history of rheumatoid arthritis and recovered from Grade 4 transaminitis after combined ipilimumab/nivolumab for melanoma. However, when she was rechallenged with ipilimumab alone she developed recurrent Grade 4 transaminitis. Although she recovered uneventfully from the transaminitis, ICI therapy was permanently discontinued. Case #1 declined ICI rechallenge due to personal preference and case #2 was offered ICI rechallenge but was lost to follow-up.

3.4 Controls with Severe IRAES (Grade 3-5)

3.4.1 Baseline Characteristics

7/9 (77.8%) controls with severe irAEs were female. The median age of the control group at cancer diagnosis was 62.0 years (IQR 46.0-71.0). The cancer histologies included lung (n = 2), urothelial (n = 2), cervical (n = 3), hepatobiliary (n = 1), and melanoma (n = 1). All (100%) had metastatic disease prior to ICI therapy (Table 1).

3.4.2 Outcomes

Of the 9 controls with severe irAEs, 4 (44.4%) had stable disease or a positive clinical response by RECIST [19]. Five of 9 (55.6%) had PD, 3/9 (33.3%) had SD, none (0.0%) had PR, and 1/9 (11.1%) achieved a CR (Figure 4).

Three of the 9 (33.3%) controls with severe irAEs developed long-term sequalae. Control #3 developed chronic arthritis requiring weekly methotrexate after receiving 3 cycles of combined ipilimumab and nivolumab for urothelial cell carcinoma. Control #4 developed chronic arthritis requiring the use of daily non-steroidal anti-inflammatories after receiving 9 cycles of pembrolizumab for cervical cancer. Lastly, control #6 developed chronic transfusion-dependent anemia after receiving 6 cycles of pembrolizumab for cervical cancer (Table 3).

Overall, 8/9 (88.9%) controls with Grade $\geq$ 3 irAEs survived the irAE. Control #5 received one cycle of nivolumab for cervical cancer and died from ICI hepatitis. Five of 5 (100%) controls who were rechallenged with ICI monotherapy were successful. Two of 9 (22.2%) controls (Control #1 and Control #9) were offered rechallenge but declined due to personal preference (Table 3).

3.5 ICI Cessation

The most common reason for discontinuation of ICI therapy was disease progression (17/28 cases, 60.7%). Other reasons were therapy completion in 6/28 cases (21.4%), immunotoxicity

in 3/28 cases (10.7%), and patient preference or relocation reasons in 2/28 cases (7.1%). ICI therapy was discontinued due to disease progression in 31/56 controls (55.4%), therapy completion in 17/56 controls (30.4%), immunotoxicity in 4/56 controls (7.1%), and other reasons in 4/56 controls (7.1%). Other reasons included patient preference, relocation, and transition to hospice.

3.6 Clinical Response & Survival Analysis

The median follow-up time among cases was 12.8 months (IQR 5.8-35.7 months). The median follow-up time among controls was 10.4 months (IQR 4.1-39.9 months). There was no significant difference in the median follow-up time between cases and controls (Mann-Whitney U = 766, $p = 0.867$, ns).

The clinical responses to ICI therapy did not differ significantly between cases and controls $X^2(3.0, 84) = 0.26$, $p = 0.967$, ns, Figure 5). Among cases, 13/28 (46.4%) had PD, 6/28 (21.4%) had SD, 6/28 (21.4%) had PR, and 3/28 (10.7%) had CR. Among controls, 29/56 (51.8%) had PD, 11/56 had SD (19.6%), 10/56 (17.9%) had PR, and 6/56 (10.7%) had CR.

Overall survival did not differ between cases and controls (Figure 6, Log-Rank $p = 0.998$, ns).

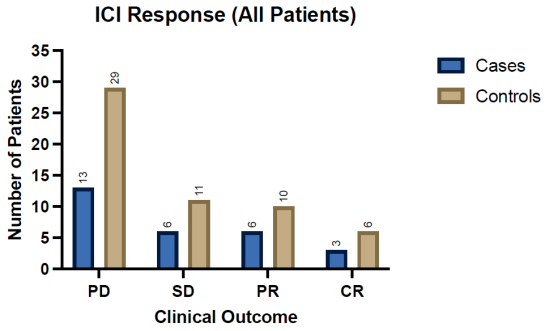

Figure 5 There was not a significant difference between type of clinical outcome among cases and controls $X^2(3.0, 84) = [0.26]$, $p = 0.967$, ns. PD: Progressive Disease; SD: Stable Disease; PR: Partial Response; CR: Complete Response.

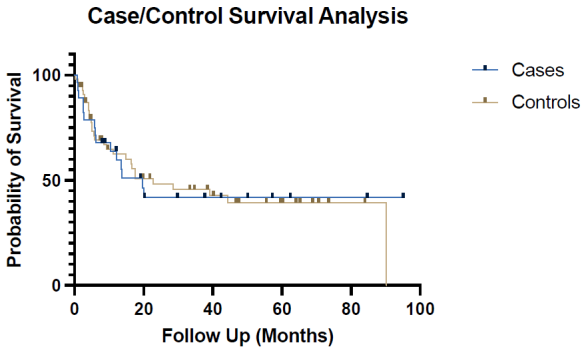

Figure 6 Overall survival of patients with pre-existing autoimmunity (cases) and matched individuals without pre-existing autoimmune disease (controls) treated with immune checkpoint inhibitor therapy ($p = 0.998$, ns, Mantel-Cox test).

4 Discussion

Given the unknown safety profile of ICIs in patients with pre-existing autoimmune conditions, we evaluated irAE incidence and severity in this population. Specifically, our study focused on individuals with pre-existing systemic, chronic autoimmune disease with detailed evaluation of clinical outcomes for both irAEs and cancer treatment. In this cohort, patients with pre-existing autoimmunity experienced irAEs at similar rates to patients without pre-existing autoimmunity when matched for sex, age, cancer type, and ICI regimen. Patients with pre-existing autoimmunity also experienced severe irAEs (Grade $\geq$ 3) at similar rates to patients without pre-existing autoimmunity. Importantly, cases and controls demonstrated similar overall survival and tumor response.

Our study's overall irAE incidence (44%) and severe irAE incidence (17.9%) are within the range of those previously reported in the literature (10-80% and 2.5-18%, respectively) [3, 4]. We matched cases 2:1 for sex, age, organ of tumor origin, and ICI class for a variety of cancer histologies and autoimmune diseases. Furthermore, all patients were treated at the same academic medical center, reducing the likelihood of significant differences in irAE recognition between groups. Thus, our study provides an important benchmark for the relative risk of all grade and severe irAEs in patients with pre-existing systemic, chronic autoimmune conditions, a population for which the use of ICI therapies has historically not been used due to irAE concerns. Prior studies, including the largest authored by Tison et al. and Pizuorno Machado et al., utilized a case series design and lacked a comparator group [20, 21]. Placais et al. recently published a similar case-control study but only in patients with melanoma [14]. Our data found no difference in the frequency of irAEs or severe irAEs and can inform discussions between providers and their patients in considering initiation of ICI cancer treatments.

Regarding ICI rechallenge success, the patients in our study were more successful in continuing ICI therapy compared to patients in prior studies. After experiencing a Grade 3-4 irAE, the majority of patients who were rechallenged with ICIs were successful in continuing therapy (66.7% of cases, 100% of controls). In other words, the irAE recurrence rate was 33.3% for cases and 0% for controls who had experienced severe irAEs. The case who was not successful in rechallenge experienced Grade 4 transaminitis, recovering with steroids. In the literature, the irAE recurrence rate after ICI rechallenge has been reported to be 18-42% [22–26]. One of the largest studies on this topic was a cross-sectional study conducted by Dolladille et al., which analyzed 24,079 irAEs and found an irAE recurrence rate of 28.8% [27]. Notably, prior studies included all-grade irAEs, while we analyzed irAE recurrence in patients with severe (Grade 3-4) irAEs. Our data support consideration of ICI rechallenge with clinically appropriate monitoring and follow-up, even in patients who have experienced Grade 3 irAEs. The 2021 American Society of Clinical Oncology guidelines recommend permanent discontinuation of ICIs in patients who have experienced Grade 4 irAEs, which align with our results [28].

One of the major strengths of our study was the variety of autoimmune conditions, cancer histologic types, and ICI therapies represented in our cases and controls. We had a variety of autoimmune conditions represented in our patient population (12 different autoimmune diseases included in our search, with seven different autoimmune diseases in cases), compared to prior studies which evaluated only one or a few autoimmune conditions [29, 30]. Rheumatoid arthritis is frequently studied [2]. Additionally, we selected patients with autoimmune diseases that have multiple systemic manifestations rather than patients with singular organ involvement, such as thyroiditis. Moreover, we had patients with a variety of cancer histologies, compared to other studies that administered ICIs primarily to patients with melanoma or NSCLC [14, 20, 31–33]. These histologies were likely selected because of the initial approval of ICI in this population, whereas ICI indications have now expanded to many cancer histologies. Therefore, as ICI indications continue to expand, evaluation of the safety of ICI in patients with autoimmune diseases and multiple cancer histologies is paramount. Lastly, we included patients receiving PD1/PD-L1 monotherapy and patients receiving combination therapy with anti-CTLA4 therapy, whereas other studies have only included patients receiving one or the other [29, 31, 33].

Another strength of our study includes automated data extraction from electronic medical records in tandem with manual chart review by physicians. ICD codes alone could only identify patients treated with ICIs. Thus, physician interpretation of oncology clinic, specialty clinic, and hospitalization records was critical in identifying specific details regarding autoimmune disease and irAEs. For example, an irAE may ultimately be ambiguous given that it is a diagnosis of exclusion based on clinical history and diagnostics. We adopted a conservative approach by having a low threshold to diagnose an irAE if it fit the clinical picture instead of requiring an irAE diagnosis to appear in oncology documentation. This was especially pertinent if patients experienced mortality or were lost to follow up, as they were not seen again by their oncologists.

We found that patients generally did not experience irAEs in the same organ affected by their autoimmune disease, which is an area of uncertainty in the literature. Studies by Pizuorno Machado et al. and Richter et al. had similar findings to ours, whereas Labadzhyan et al. found that serum endocrine-specific antibodies were found in patients with endocrine irAEs [21, 34, 35]. We also describe the cancer outcomes of our cases and controls and did not find a significant difference in cancer response between cases and controls. While the literature suggests that patients who experience irAEs have a more robust tumor effect from ICIs compared to patients without irAEs, we did not see this in our cohort, possibly because of a biologic difference in patients with autoimmune disease as suggested by Abdel-Wahab et al., or because of our small sample size [12, 36]. In our cohort, overall survival was similar between cases and controls,

which differs from the findings of Placais et al., who found improved overall survival in the autoimmune disease group [14]. This difference may be related to Placais et al.'s focus on patients with melanoma, a cancer histology that is very responsive to ICIs, whereas our cohort included all cancer histologies.

Our study was limited by its retrospective nature, single-center design, and small sample size. The retrospective nature inherently limits causal inference. While our center is a large, urban, academic medical center, the single-center nature limits broad generalizability. We attempted to control for confounding variables with 2:1 matching of controls to cases by sex, age, cancer type, and ICI class. Additionally, our sample size was small, although we were limited by the small number of patients with pre-existing autoimmunity receiving ICI therapy due to safety uncertainties in the literature. We used a large database (N = 3,130) to identify patients and found 28 cases who had been treated with ICIs. Matching cases to controls increased the power of the study given our small case number.

5 Conclusion

These results augment the sparse literature on this topic and suggest that ICIs may be considered as a reasonable cancer treatment option for patients with pre-existing systemic autoimmunity. This is a particularly vulnerable patient population that has historically been excluded from ICI trials due to clinical uncertainty, and, therefore, physicians are understandably hesitant to administer ICIs to these patients. Current guidelines from the National Comprehensive Cancer Network are limited for this population; they recommend that oncologists consider anti-PD1/PD-L1 monotherapy rather than combination therapy and optimize immunosuppression with a goal of $<$ 10 mg of prednisone daily prior to ICI initiation [37]. The results of this study have the potential to expand available safety and efficacy data for this critical treatment option for many malignancies in this population. Nevertheless, this knowledge must ultimately be paired with an oncologist's patient-centered discussion incorporating potential immunotherapy risks.

Continued studies to identify the optimal balance of anti-tumor efficacy and toxicity with cancer immunotherapies are needed. We await the results of prospective studies to answer some of these questions, including an ongoing phase Ib trial of nivolumab for patients with autoimmune disease and advanced malignancy sponsored by the National Cancer Institute [38].

Lastly, paired with these clinical studies, translational studies of irAE mechanisms will facilitate the development of potential therapeutic strategies to facilitate safer use of ICI treatments in a broader group of cancer patients.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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PERSPECTIVE

Perspectives on chemotherapy-induced toxicities in pancreatic cancer

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Abstract: Despite breakthroughs in screening, identification, and therapy, pancreatic cancer (PC) remains a serious issue in cancer-related mortality. This comprehensive review investigates the long-term and latent effects of chemotherapy in PC, focusing on commonly used medicines such as gemcitabine, docetaxel, irinotecan, nab-paclitaxel, and others. Gemcitabine, a common PC medication, causes a variety of adverse effects, including myelosuppression and weariness. Combination therapy, such as docetaxel and irinotecan, enhance toxicity, resulting in problems such as neutropenia and gastrointestinal difficulties. Significantly, chemotherapy-related complications, such as thrombosis and cardiac difficulties connected to paclitaxel, present serious concerns. Erlotinib, gefitinib, vatalanib, and sunitinib studies show significant side effects. Despite ongoing challenges, determining the causes of the low objective response rate in gemcitabine-refractory patients remains challenging. The study emphasizes the importance of future advances in cancer etiology, arguing for large, straightforward studies examining combination chemotherapies to improve tolerance and minimize chemotherapy-induced sequelae. This overview serves as a thorough guide for physicians, researchers, and policymakers as they navigate the complex terrain of PC chemotherapy, providing significant insights to improve patient care.

Keywords: pencretic cancer, chemoresistance, toxicities

Despite tremendous progress made in screening, detection, and treatment, pancreatic cancer (PC) is ranked in the fourth position among cancer-related deaths in United States [1]. It is projected that with improved treatment and early detection, the number of all cancer survivors will increase to over 20 million by 2026 [2]. According to GLOBOCAN 2016, almost 340,000 new cases of PC are diagnosed each year worldwide and PC is responsible for 331,000 deaths/year [3]. Chemotherapy is common treatment for all cancers that have extend from the primary tumor site. However, drug resistance to chemotherapy is a major impediment to patient survival and the leading cause of death in patients of the most advanced stage [4–6].

Over the last few decades, many anticancer therapies have been tested in the locally advanced and metastatic setting with reported mixed results. Many of these cancer survivors have long-term and latent effects from their treatment. Despite the improved efficacy and improved survival offered by modern treatments, the toxic side effects and long-term squeal of chemotherapy remain a major source of concern for both patients and clinicians. In this perspective, we summarize the common long-term and latent treatment effects for PC. During the treatment of PC patients, doctors use various cytotoxic drugs and the side effects vary from one drug to another. Patients may experience various side effects during PC treatment detailed in Table 1.

Gemcitabine monotherapy has been the standard of care for patients with PC since 1997 when it was shown to improve survival compared to 5-fluorouracil (5-FU) [7]. The common side effects of gemcitabine includes poor appetite, nausea, vomiting, diarrhea, myelosuppression, elevated liver enzymes, edema, rash, mouth sores, hair loss, sometimes change in liver or kidney function and extreme fatigue. The initial toxic effect of gemcitabine (1,000 mg/m^2 administration once weekly for 3 out of every four weeks) in PC has been demonstrated by Min et al. in 17 chemotherapy patients; they observed that the one-year survival rate was 18 % and is associated with both grade 3-4 leucopenia in 29% of patients [8].

A pilot study using the combination of docetaxel (65 mg/m^2) and irinotecan (160 mg/m^2) given on a 21-day cycle is associated with excess toxicity, mainly neutropenia, diarrhea, nausea

Table 1 Chemotherapeutic drugs, their chemical essence, side effects, frequency and their significance for pancreatic cancer treatments

Chemo Drug	Chemical essence	Side Effects	Frequency	Significance	Reference
Gemcitabine	Nucleoside analog	Nausea, low blood counts, fatigue Liver abnormalities	Common Less Common	Standard chemotherapy for PC, used alone or in combination for advanced or metastatic cases.	[9]
FOLFIRINOX (5-FU, Leucovorin, Irinotecan, Oxaliplatin)	DNA synthesis inhibitor & Topoisomerase inhibitor	Diarrhea, neuropathy, neutropenia	Common	A combination therapy more aggressive than gemcitabine alone, used for metastatic pancreatic cancer in patients with good performance status.	[10]
Nab-Paclitaxel + Gemcitabine	Microtubule inhibitor	Neuropathy, fatigue, hair loss	Common	Combination used for the treatment of metastatic PC, improving survival rates over gemcitabine alone.	[11]
Erlotinib (Tarceva)	EGFR pathway	Rash, diarrhea Interstitial lung disease	Common Rare	Combination with gemcitabine for advanced PC, offering a modest survival benefit by targeting the EGFR pathway	[12]
Capecitabine	Thymidine synthesis inhibitor (Pyrimidine analog)	Hand-foot syndrome, diarrhea, nausea, vomiting Neutropenia, fatigue, abdominal pain Cardiotoxicity (chest pain, arrhythmias, etc.)	Common Common Less Common	An oral drug that metabolizes into 5-FU in the body, sometimes used in combination therapies	[13]

and vomiting in gemcitabine-refractory patients with advanced PC [14]. People receiving chemotherapy also are more likely to have low levels of white blood cells, red blood cells, and platelets leading to higher risk of anemia, infections, and hemorrhage [15]. In a phase I/II clinical trial on patients receiving 1,000 mg/m^2 of gemcitabine plus 125 mg/m^2 of *nab*-paclitaxel once a week for three weeks, showed sepsis and neutropenia toxicities. The most common grade 3-4 toxicities are fatigue, sensory neuropathy, and hematological toxicities including neutropenia, leukopenia, and thrombocytopenia [16].

Cancer can increase the risk of developing a blood clot known as thrombosis, and the chemotherapy may increase further risk of thrombosis. The cardiovascular complications such as venous thromboembolism, acute arterial events, and systemic capillary leak syndrome are common in cancer chemotherapy. A blood clot can cause chest pain and discomfort, redness, and swelling in a leg or arm, as well as shortness of breath. Paclitaxel is a microtubule-targeting anti-cancer agent that can result in cardiac problems. A study suggests that gemcitabine plus nab-paclitaxel is associated with congestive heart failure in advanced PC [17]. Paclitaxel, in combination with doxorubicin, also caused hypersensitivity neurotoxicity and palmar-plantar erythrodysesthesia in PC patients [18]. Peripheral neuropathy is observed as a side effect of nab-paclitaxel as well.

A combination treatment of raltitrexed and irinotecan in patients with gemcitabine-pretreated advanced PC showed adverse effects related to gastrointestinal, partial alopecia, and cholinergic syndrome [19]. Other studies also find similar results to neutropenia, fatigue, and diarrhea symptoms in gemcitabine-refractory metastatic PC treated with docetaxel 35 mg/m^2 followed by flavopiridol 80 mg/m^2 on days 1, 8, and 15 of a 28-day cycle [20]. Further, in metastatic PC patients, a gemcitabine containing regimen with pemetrexed 500 mg/m^2 as a 10-min infusion every three weeks showed hematological toxic effects including neutropenia, thrombocytopenia and anemia and non-hematological toxic effects such as diarrhea, nausea and stomatitis/pharyngitis [21]. The combination of 125 mg/m^2 of lipoplatin (liposomal cisplatin) and 1000 mg/m^2 of gemcitabine in advanced PC patients showed neutropenia as a primary symptom [22]. Gemcitabine + cisplatin combination in patients with advanced PC showed anemia or blood loss as the major adverse effects [23].

The erlotinib, an oral tyrosine kinase inhibitor (TKI) targeting the epidermal growth factor receptor (EGFR), is effective against PC [24, 25]. In gemcitabine resistance patients, the combination of capecitabine (1,000 mg/m^2) and erlotinib (150 mg) shows significant toxicity of diarrhea and skin rashes [26]. In patients pretreated with gemcitabine-based chemotherapy, combination of docetaxel (75 mg/m^2) and gefitinib (250 mg/day) administered every 3 weeks for a maximum of 6 cycles of treatment revealed neutropenia, fatigue, febrile, rash and diarrhea as common side effects [27]. The combination of gefitinib (250 mg/day orally) and docetaxel (75 mg/m^2) for 21 days caused major febrile neutropenia, with fatigue, nausea, diarrhea and vomiting as common adverse effects [28]. Vatalanib is another oral poly-tyrosine kinase inhibitor targeting vascular endothelial growth factor (VEGF) receptors. Phase II trial of Vatalanib in PC patients who failed first-line gemcitabine-based therapy, showed significant symptoms of hypertension, fatigue, abdominal pain, and elevated alkaline phosphatase level [29]. The sunitinib, a multi-target TKI used to treat advanced PC patients with a dose of 50

mg daily for 28 days. Sunitinib treatment in PC patients pretreated with gemcitabine-based chemotherapy showed severe fatigue, bleeding, nausea 4%, thrombosis / embolism, thrombotic thrombocytopenic purpura / renal failure, GI perforation and hematologic complication [30].

However, the exact reasons for the low objective response rate in PC patients who are refractory to gemcitabine are not fully known.

Gemcitabine refractory individuals, or those who do not respond to the chemotherapeutic medication gemcitabine, are commonly encountered in clinical practice, particularly in the treatment of PC. Gemcitabine has been a cornerstone of PC therapy, however resistance to this medicine is a substantial obstacle, typically resulting in restricted treatment alternatives and a poor prognosis for these patients. Gemcitabine resistance mechanisms are complicated and multidimensional; comprising changes in drug uptake and metabolism, apoptosis evasion, and activation of alternative survival pathways such as the Akt/mTOR pathway [31].

A subsequent study demonstrated that mTOR inhibitors were incapable of eliciting an objective response or disease stability, but rather created a negative feedback loop that resulted in disease progression and toxicity [32]. The Akt/mTOR pathway contributes to gemcitabine resistance in PC due to Annexin II, suggesting mTOR inhibitors could counteract this resistance [33]. Additionally, the PI3K-AKT-mTOR pathway and immunotherapies are under clinical investigation, reflecting the diverse nature of the disease [34]. Late-onset gemcitabine-induced severe pulmonary toxicity (GISPT) progresses rapidly, with death rates of 20%. Many studies reported that GISPT significantly impacts the early mortality of PC patients with pneumonia and veno-occlusive disease [35–37].

A recent large network meta-analysis demonstrated that FOLFIRINOX and Gemcitabine Pemetrexed regimens have a relatively higher incidence of toxicity in PC [38]. Certain chemo-drugs used to treat PC have also been linked to adverse effects, including capecitabine, which can cause hand-foot syndrome, and oxaliplatin, which can cause peripheral neuropathy. The timeline depicted in Figure 1 illustrates the evolution of pancreatic cancer chemotherapeutic agents.

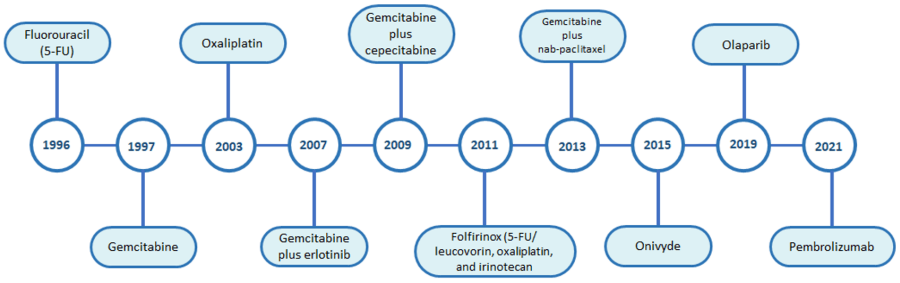

Figure 1 The time line of advancement in chemotherapeutic agents in advanced pancreatic cancer

Despite multiple clinical trials and continuous efforts, PC remains one of the most challenging cancers to cure because of its aggressive characteristics and resistance to conventional chemotherapy. However, with advancements in early detection and treatment, cancer survivorship is expected to increase by 5 million globally over the next decade [39].

The presence of such resistance mechanisms necessitates the investigation of alternative therapeutic strategies, such as combination therapies that target the underlying resistance pathways, the use of newer chemotherapeutic agents, and the incorporation of targeted therapies and immunotherapies into treatment plans. Recent research and ongoing clinical trials are aimed at identifying predictive biomarkers that can help guide the selection of targeted medicines for particular patients, resulting in a more personalized approach to treatment [40]. This technique aims to enhance outcomes for gemcitabine-resistant individuals by personalizing therapy to the specific molecular profile of their tumor.

Although current drugs or other approaches to counteract chemotherapy-induced adverse effects are often incompletely effective, they frequently do not address potential longer-term sequelae or even induce other side effects, which only add to patient discomfort. In this context, advancements in cancer treatment require an increased understanding of cancer pathogenesis, mainly how cancer evolves. Further, preclinical and clinical studies with large simple trials using combination chemotherapies can be a promising approach to improve tolerance and reduce squeal of cancer chemotherapy.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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RESEARCH ARTICLE

Breast carcinoma in the Democratic Republic of the Congo: Characterization of hormone receptors

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Abstract: Purpose: Breast cancer is a heterogeneous disease, and understanding its characteristics is crucial for effective treatment. Therefore, this study aims to investigate breast carcinomas as a function of hormone receptors (estrogen and progesterone) in the Democratic Republic of the Congo (DRC), which can contribute to better management of breast cancer cases in the country. **Methods:** We conducted an analytical cross-sectional study from 2014 to 2016 in the cities of Kinshasa and Lubumbashi. Using non-random sampling, we collected 86 cases of breast carcinoma. **Results:** The study found that out of the 86 cases of breast carcinoma, 33 patients (38.3%) had both types of hormone receptors (ER+/PgR+), while 37 patients (43.0%) had negative results for both receptor types (ER-/PgR-). Additionally, 15 patients (17.4%) had only estrogen receptors. The study did not find any significant association between the presence of estrogen receptors and patient age, T stage, histological type, and Ki67 proliferation index. However, the study did observe that estrogen receptors were significantly more present in grade I and II tumors (74.4%) than in grade III tumors (40.4%) (OR = 4.3 [1.7-10.8]; p = 0.003). **Conclusion:** The findings of this study demonstrate a high prevalence of hormone receptors in breast cancer cases in the DRC. Additionally, the study revealed a significant association between the presence of estrogen receptors and tumor grade, underlining the relevance of these markers in the characterization and treatment of the disease.

Keywords: carcinoma, breast cancer, hormone receptors

Abbreviations

DRC: Democratic Republic of the Congo
ER: estrogen receptor
IHC: immunohistochemistry
NST: no specified type
PgR: progesterone receptor

1 Introduction

Breast cancer is a major public health concern worldwide, affecting millions of people each year [1]. As a complex and heterogeneous disease, it presents a varied range of forms, each with unique implications for diagnosis, prognosis, and treatment [2]. To date, there is no standard management plan that is effective for all forms of breast cancer. A majority of breast tumors (50-80%) are classified as invasive ductal carcinoma no specified type (NST) [3] due to their inability to be categorized into one of the other 20 subtypes [4]. Hormone receptors, such as estrogen receptors (ER) and progesterone receptors (PgR), play a critical role in the classification of breast cancer, influencing the decision-making process for treatment options. ER and PR are proteins that bind to hormones within cells, initiating changes within the cell. Hence, this classification is crucial in the management of the disease [5]. The presence or absence of hormone receptors such as ER and PgR can significantly affect the course of treatment of breast cancer, often determining the success or failure of hormone therapy. These receptors also provide critical information on the prognosis of the disease, including the aggressiveness of the cancer, the patient's survival rate, and the likelihood of recurrence [6]. Therefore, healthcare

professionals and patients must understand this classification to effectively manage breast cancer, which remains a significant public health challenge worldwide.

However, the presence of these hormone receptors varies from study to study. For instance, a Togolese study found 54.7% and 41% for estrogen and progesterone receptors respectively [6]. In the Democratic Republic of the Congo (DRC), a recent study by Sulu *et al.* [7] of 190 women with breast cancer reported that 85.26% and 77.37% of cases respectively. Despite the seriousness of this health problem, there is a notable lack of in-depth research and studies into the specific characteristics and nuances of this disease in the DRC, particularly with regard to the role and influence of hormone receptors [8]. As highlighted in the previous paragraph, hormone receptors play a crucial role in the categorization, prognosis and treatment of breast cancer, and understanding their role and prevalence in the DRC could lead to more effective treatment strategies and better patient outcomes.

The aim of this study is to describe the hormone receptors found in women with breast carcinoma in the DRC. The importance and potential impact of this study are underlined by its potential implications for the therapeutic approach and prognosis of breast cancer in the DRC.

2 Materials and methods

An analytical cross-sectional study was conducted between 2014 and 2016 in the cities of Kinshasa and Lubumbashi, including 86 patients with histologically confirmed localized breast cancer. We excluded patients with non-epithelial tumors, secondary tumors, metastatic forms from the outset, and localized breast carcinomas with synchronous tumors of digestive, hepatic, or other origin whose records could not be used.

Data was collected from medical records, focusing on variables such as patient age, TNM classification, treatment modalities, progression, and date of last news. Histological data were obtained from anatomopathological reports, including histological type, tumor size, lymph node status, Scarff-Bloom-Richardson (SBR) histopronostic grade modified by Elston and Ellis, and histological evaluation of chemotherapy from immunohistochemical reports (estrogen receptors, progesterone receptors, and Ki67 index).

Immunohistochemistry (IHC) was performed in Germany at Martin-Luther-University. Mouse monoclonal antibodies were used. For ER, clone 1D5 (Zytomed Systems, Berlin, Germany) was used. For PgR, clone 636 (Dako, Carpinteria, CA) was used. For HER2/neu, Hercep Test (Dako) was used. Clone MSK018 (Zytomed System GmBH BERLIN, Germany) was used for Ki67. These tests were performed using a semi-automated system (intelliPath; BiocareMedical, Pacheco, CA). ER and PgR were considered positive if nuclear impregnation was $>1\%$. A cut-off of 20% was used for Ki67.

The data were analyzed using SPSS23 software. Qualitative variables were presented in the form of frequencies. The Chi-square test was used to compare frequencies, and the odds ratio and its 95% confidence interval were calculated. The significance threshold was set at $p<0.05$.

3 Results

A total of 86 patients were included in the present study. The mean age of the patients was 48 years, with a range of 23 to 86 years. Of the patients, 36 (41.9%) were aged 50 years or older, and 2 (2.3%) were aged under 30 years. (see in Table 1)

According to T staging, the tumor was classified as T1 in 1.2% of cases, T2 in 24.4% and T3 in 54.7%. Histologically, invasive ductal carcinoma was the most common histological type (97.6%), associated with a lobular component in 1.2% of cases. The number of histological grade II and III tumors was high (40.7% and 54.7% respectively). We found that, immunohistochemically, ER were positive in 55.8% of patients and PgR were positive in 39.5%. The Ki67 proliferation index was >20 in 57.0% of cases.

Patients with both types of hormone receptor (ER+/PgR+) accounted for 38.3% (33/86), while patients with both types of hormone receptor negative (ER-/PgR-) accounted for 43.0% (37/86); 17.4% (15/86) of patients had only ERs (Figure 1).

Table 2 displays the correlations between patient characteristics and the presence of ER. We found no significant association between the presence of ER and patient age, T stage, histological type, and Ki67 proliferation index. However, we observed that ER were more present in grade I and II tumors (74.4%) than in grade III tumors (40.4%) (odds ratio = 4.3 [1.7-10.8]; p = 0.003).

Table 1 Age, clinical, and immunohistochemical characteristics of 86 patients

Variable	Number (n = 86)	Percentage (%)
Age		
<30 years	2	2.3
30-39 years	23	26.7
40-49 years	25	29.1
≥ 50 years	36	41.9
T Staging		
T1	1	1.2
T2	21	24.4
T3	64	74.4
Histological grade		
I	4	4.6
II	35	40.7
III	47	54.7
Histological type		
Invasive ductal carcinoma	84	97.6
Mixed invasive ductular and lobular carcinoma	1	1.2
Invasive papillary carcinoma	1	1.2
Estrogen receptors		
Present	48	55.8
Absent	38	44.2
Progesterone receptors		
Present	34	39.5
Absent	52	60.5
Ki67 proliferation index		
≤ 20	37	43.0
>20	49	57.0

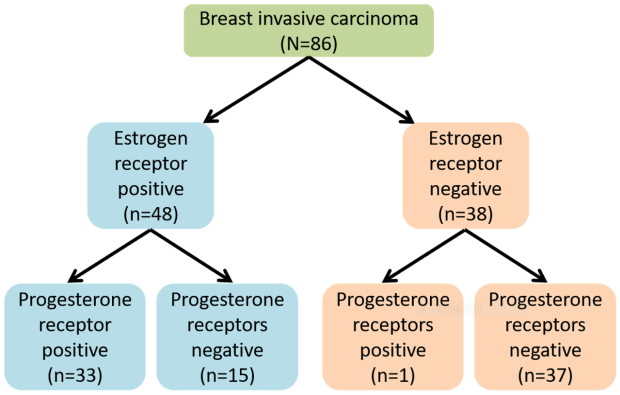

Figure 1 Distribution of patients with breast cancer according to estrogen and progesterone receptors

Table 2 Clinical-histological factors influencing the presence of estrogen receptors (ER)

Variable	ER positive (n = 48)		ER negative (n = 38)		OR [95% CI]	p-value
	n	%	n	%		
Age						
≤45 years	23	60.5	15	39.5	1.4 [0.6-3.3]	0.573
>45 years	25	52.1	23	47.9	1.0	
T Stage						
T1/T2	15	66.7	7	33.3	2.0 [0.7-5.6]	0.269
T3	33	51.6	31	48.4	1.0	
Histological grade						
I/II	29	74.4	10	25.6	4.3 [1.7-10.8]	0.003
III	19	40.4	28	59.6	1.0	
Histological type						
Invasive ductal carcinoma	46	54.8	38	45.2	1.0	
Mixed invasive ductular and lobular carcinoma	1	100	0	0	ind.	1.000
Invasive papillary carcinoma.	1	100	0	0	ind.	1.000
Ki67 proliferation index						
≤20	24	64.9	13	35.1	1.9 [0.8-4.6]	0.211
>20	24	49	25	51	1.0	

4 Discussion

Antihormonal treatments have significantly improved the treatment of breast cancer, reducing the need for surgery or radiotherapy [9]. The study used immunohistochemical techniques to determine the expression of nuclear hormone receptors in breast cancer patients in the DRC. The majority of patients (55.8%) had positive expression for at least one hormone receptor, indicating a significant representation of this characteristic. However, a high proportion of cases (43%) were without hormone receptors (ER-/PgR-), indicating the diversity of breast carcinoma subtypes and the high prevalence of triple-negative carcinoma subtypes in this population.

Hormone dependence is present in 38.3% of cases (ER+/PgR+), uncertain in 17.4% (ER+/PgR-), and absent in 43.0% (ER-/PgR-). PgR expression is crucial for prognosis, as it indicates a functional estrogenic pathway as PgR are induced by the ER [10]. The ER+/PgR- phenotype has a poorer prognosis due to transcriptional down-regulation of the ER, resulting in reduced efficacy with antiestrogen treatment [11]. The presence of ER-/PgR+ tumors is a topic of debate, as they represent only 1.1% of cases in this study and are considered an artefact. Some experts believe tamoxifen may be effective in treating ER-/PgR+ tumors [12, 13].

Hormone receptors were found in 55.8% of cases in this study, contrasting with studies conducted on white women, where hormone dependence is estimated to be over 70% [13, 14]. This is consistent with studies on African women, where hormone receptor negativity ranges from 22% to 35% in East Africa [15–17] and 44% to 80% in West Africa [18–20]. McCormack et al's [21] study in South Africa found that 35% of cases were hormone receptor negative. In the United States, 39% of black American women were hormone receptor negative, compared to 16% of Caucasian women [22]. In China, ER- tumors are estimated at 21.6% [23], while in India/Pakistan at 30.6% [24]. The study found similar results in West Africa and the United States for black American women, possibly due to shared hereditary heritage, eating habits, and reproductive habits among American women of African origin and patients from West and Central Africa, and the history of the slave trade.

The age at which someone is considered 'young' is not widely agreed upon, but studies have shown hormone receptors are more frequent in older individuals, while younger people tend to present non-hormone-dependent forms [25, 26]. This study found more ER+ tumors in individuals under 45, but no significant differences were found between age groups and hormone receptor presence or absence. The NST sub-group comprises heterogeneous tumors with variable phenotypes, including mixed ductular and lobular invasive carcinoma and papillary invasive carcinoma [27]. The study found a significant correlation between tumor grade and hormone receptor presence. Past research has demonstrated that less differentiated tumors are more likely to be non-hormone-dependent [11, 19, 28]. The histological grade, which incorporates the mitotic index, measures cell proliferation, and ER- tumors, often grade III and having a high mitotic index, are more proliferative [11].

Compared to stage T3, the study reveals that there are more ER+ tumors and fewer ER- tumors at stages T1 and T2. This difference is not statistically significant, but it could be due to factors such as non-accessibility to care, the high proliferative nature of ER- tumors, and the biological characteristics of the tumor, particularly the expression of hormone receptors. It is understandable that these tumors are often large and diagnosed at an advanced stage [29, 30]. Patients who delay consultation may experience changes in their tumor's biological characteristics [31]. Some authors argue that grade I and grade III tumors are different diseases with different activation pathways, and do not progress from grade I to grade III after a certain period [28]. The proportion of ER+ tumors decreases with increasing histological grade, possibly due to accelerated growth of ER- tumors due to loss of estrogen expression in advanced forms of the disease. ER- tumor status is most likely a false negative due to the failure to obtain a biopsy from the original ER+ tumor. African studies suggest the advanced stage of cancer at diagnosis and the predominance of ER- forms [28, 31]. Time can modify the characteristics of a tumor through the accumulation of genetic mutations, which can have repercussions on the phenotype.

5 Conclusion

The study reveals a wide range of hormone receptors, particularly estrogen and progesterone receptors, with almost half of cases being negative. The presence of estrogen receptors is significantly associated with tumor grade, with a predominance in grade I and II tumors. Accurate characterization of breast tumors is crucial for treatment decisions and patient outcomes.

Enhancing early breast cancer screening programs, improving tumor characterization techniques like immunohistochemistry, and improving access to targeted hormone therapy are also necessary. Further research is needed to understand the factors driving hormone receptor diversity and their impact on tumor progression, which could guide better breast cancer prevention and treatment strategies in the DRC.

Conflicts of interest

The authors declare that they have no conflict of interest.

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