

Effect of a multidisciplinary Severe Immunotherapy Complications Service on outcomes for patients receiving immune checkpoint inhibitor therapy for cancer

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ABSTRACT

Background In 2017, Massachusetts General Hospital implemented the Severe Immunotherapy Complications (SIC) Service, a multidisciplinary care team for patients hospitalized with immune-related adverse events (irAEs), a unique spectrum of toxicities associated with immune checkpoint inhibitors (ICIs). This study's objectives were to evaluate the intervention's (1) effect on patient outcomes and healthcare utilization, and (2) ability to collect biological samples via a central infrastructure, in order to study the mechanisms responsible for irAEs.

Methods A hospital database was used to identify patients who received ICIs for a malignancy and were hospitalized with severe irAEs, before (April 2, 2016–October 3, 2017) and after (October 3, 2017–October 24, 2018) SIC Service initiation. The primary outcome was readmission rate after index hospitalization. Secondary outcomes included length of stay (LOS) for admissions, corticosteroid and non-steroidal second-line immunosuppression use, ICI discontinuation, and inpatient mortality.

Results In the pre-SIC period, 127 of 1169 patients treated with ICIs were hospitalized for irAEs; in the post-SIC period, 122 of 1159. After SIC service initiation, reductions were observed in irAE readmission rate (14.8% post-SIC vs 25.9% pre-SIC; OR 0.46; 95% CI 0.22 to 0.95; $p=0.036$) and readmission LOS (median 6 days post-SIC vs 7 days pre-SIC; 95% CI –16.03 to –0.14; $p=0.046$). No significant pre-initiation and post-initiation differences were detected in corticosteroid use, second-line immunosuppression, ICI discontinuation, or inpatient mortality rates. The SIC Service collected 789 blood and tissue samples from 234 patients with suspected irAEs.

Conclusions This is the first study to report that establishing a highly subspecialized care team focused on irAEs is associated with improved patient outcomes

and reduced healthcare utilization. Furthermore, the SIC Service successfully integrated blood and tissue collection safety into routine care.

BACKGROUND

As of November 2020, there are 55 Food and Drug Administration-approved indications for immune checkpoint inhibitors (ICIs) in the treatment of cancer.¹ Concordant with the increase in approvals, the number of patients eligible for ICI therapy has exponentially grown; whereas only 1.5% of patients with cancer were eligible for ICI therapy in 2011, by 2019 the percentage had risen to 36% or 233,790 patients annually.² The actual number of patients treated with ICIs may be underestimated as a result of new approved indications and enrollment in clinical trials, and this number will continue to increase as new ICIs and combination immune and non-immune treatment regimens are developed.^{3 4} Despite these successes, ICI therapy may be associated with the development of treatment-related toxicities—called immune-related adverse events (irAEs)—which are thought to reflect autoinflammatory sequelae of immune activation and downstream effects that occur with ICI administration.^{5 6} In clinical trials, approximately 60%–85% of participants receiving single-agent ICI therapy develop irAEs (of any grade), with even higher numbers for those administered combination therapy.^{7–14} Approximately 10%–30%

of participants develop grade ≥ 3 irAEs,⁷ with a recent meta-analysis reporting 14% with programmed death-1 (PD-1) single agent, 34% with cytotoxic T-lymphocyte antigen-4 (CTLA-4) monotherapy and as high as 55% with combination ICI therapy.⁸ These serious toxicities may require hospitalization and high-dose immunosuppression. To date, the molecular mechanisms responsible for irAE development remain poorly understood, and we currently lack predictive markers to identify individuals at risk of developing these toxicities, which are fatal in 0.4%–1.2% of patients.¹⁵ As ICI therapy becomes a core pillar of cancer care, the incidence of irAEs will significantly increase alongside ICI use. Therefore, it is essential that the healthcare community is aware of and educated on the identification and management of irAEs.

Managing irAEs represents a major clinical challenge in oncologic care, even in large academic centers.^{16–17} Although the dermatological, gastrointestinal (GI), endocrine, and hepatic systems are most commonly involved, any organ system can be affected,⁹ and different subspecialist consultations may be required for each specific organ toxicity.¹⁰ The National Comprehensive Cancer Network (NCCN) currently recommends subspecialty consultation for (1) grade ≥ 2 colitis, hepatitis, or pancreatitis; (2) grade ≥ 2 pneumonitis; (3) grade ≥ 2 renal failure; (4) moderate myositis; (5) myasthenia gravis; (6) hyperglycemia >200 , primary adrenal insufficiency, or hypophysitis; (7) mild eye changes; (8) grade 3 or 4 rash; and (9) for any potential cardiac toxicity. Moreover, it is critical that irAEs be detected early¹⁸ through proper assessment and diagnostic testing, and that specialist care be coordinated rapidly to prevent irAEs from progressing to more severe grade ≥ 3 events. In recent years, several institutions have described the multidisciplinary team approaches they have developed for responding to irAEs.^{19–21} However, the effect of such approaches on healthcare utilization and patient outcomes has not yet been reported.

In addition, the molecular mechanisms driving treatment-induced toxicity are poorly understood, in part because it has been challenging to study irAEs using mouse models.^{22–23} An improved understanding of the mechanisms underlying irAEs development and the identification of predictive biomarkers may allow for improved management protocols and even preventive strategies for these toxicities.^{5–24–25} Our lack of mechanistic understanding of irAEs has led experts in the field to call for international registries and translational efforts to collect real-world data on irAEs.⁵

In October 2017, the Massachusetts General Hospital (MGH) altered the inpatient oncology clinical practice model to implement the Severe Immunotherapy Complications (SIC) Service—a service dedicated to caring for patients with suspected serious irAEs. This multidisciplinary effort was launched by medical oncologists who partnered with dedicated subspecialty expert consultants from 11 subspecialties to refine the clinical identification and management of irAEs. In addition to providing

clinical care, the SIC Service also supports a clinical–translational research effort to study these novel toxicities. To achieve the translational goals, a standardized infrastructure was implemented that enrolls patients with suspected irAEs into studies focused on the collection of relevant clinical data and paired blood and tissue specimens.

Here, we present data on the SIC Service’s multidisciplinary clinical and translational research effort with the goals of (1) evaluating this intervention’s effect on healthcare utilization and outcomes for patients experiencing irAEs; and (2) determining the feasibility of using a central infrastructure to collect blood and tissue samples to study the mechanisms responsible for irAEs across toxicity types.

METHODS

Study population

Using pharmacy and hospital admission databases, a list of patients was identified who received ICI (ipilimumab, pembrolizumab, nivolumab, atezolizumab, durvalumab, avelumab, or any ICI combination) for a malignancy and were hospitalized at MGH between April 2, 2016 and October 24, 2018. The start date, April 2, 2016, was selected to maintain consistency of data storage as that was the implementation date of the new EPIC electronic medical record at MGH. The SIC Service was established on October 3, 2017 and patients whose admission and discharge dates spanned this date were excluded from analysis. To ensure at least a 1-year follow-up, October 24, 2018 was chosen as the end date. The ‘pre-SIC period’ was therefore defined as an admission between April 2, 2016 through October 3, 2017 (before SIC Service implementation), and the ‘post-SIC period’ was defined as an admission from October 3, 2017 through October 24, 2018 (after SIC service implementation).

Data collection

Admissions underwent a two-stage review process where each hospitalization was first screened for the presence of a potential irAE based on documentation in the electronic health record. Subsequently, specialists (allergy: JRF; cardiology: TGN, DZ; dermatology: STC; endocrinology: ATF, MR; gastroenterology/hepatology: MD, MFT; hematology: RSKL; nephrology: MES; neurology: ACG; pulmonology: DO, BDM; rheumatology: MN, MK, SS) followed published organ-specific diagnostic criteria to identify cases of suspected or confirmed irAEs admitted to the hospital.²⁶ In patients with multiple confirmed toxicities, the primary irAE was defined as that which prompted hospitalization and/or determined treatment.

SIC Service intervention

On October 3, 2017, the SIC Service was established to care for patients hospitalized with severe irAEs. All patients who present to MGH with suspected irAEs are evaluated by 1 of 12 SIC Service oncologists with expertise in irAEs. SIC oncologists coordinate patient care with ward services and

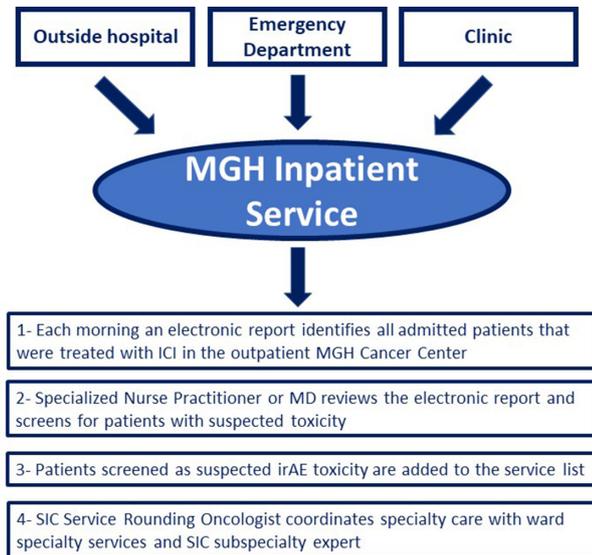


Figure 1 Patient identification for Severe Immunotherapy Complications (SIC) Service. ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; MD, Doctor of Medicine; MGH, Massachusetts General Hospital.

expert subspecialists that belong to the broader SIC Service care team and represent providers in allergy/immunology, cardiology, dermatology, endocrinology, gastroenterology, hematology, nephrology, neurology, ophthalmology, pulmonology, and rheumatology. Since the time the SIC Service began, efforts have been made to inform all emergency department providers, hospitalists, trainees, internal medicine physicians, and MGH Cancer Center providers of this team of subspecialists with irAE expertise so that patients with suspected toxicity can be referred accordingly. All admitted patients are then captured by an electronic report generated every morning that identifies all patients treated with ICIs

admitted to any floor of the hospital. Every morning, these patients' charts are reviewed for suspected toxicity by a nurse practitioner or an oncologist and added to the SIC Service list if there is clinical suspicion of toxicity (figure 1). On discharge, patients are scheduled for outpatient follow-up with the disease-specific subspecialist, when appropriate, as well as the oncologist. Finally, referrals to outpatient subspecialty clinics are streamlined to permit urgent evaluation with irAEs experts in order to avoid hospitalization when possible.

Translational research program

Under the SIC Service's translational research infrastructure, patients with suspected irAEs are identified, communicated to research staff, and consented for blood and tissue collection to occur alongside preplanned diagnostic or therapeutic procedures (figure 2). For a subset of patients, sequential specimens are collected at various points during their toxicity course including at the time of presentation before initiation of immunosuppressive therapy, diagnosis, after immunosuppression initiation and/or escalation, and at time of irAE resolution or recurrence. In specific cases of irAE, the SIC Service partners with the MGH Rapid Autopsy program (principal investigator: DJ) to collect blood as well as tissue specimens immediately after death from tumor and all involved irAE sites. All specimens are immediately couriered to the laboratory for processing and storage on the day of collection.

Primary and secondary outcomes

The primary outcome in the study was the rate of hospital readmissions for irAEs in the pre-SIC and post-SIC periods. Secondary outcomes included length of stay (LOS) for both initial irAE admissions and readmissions, use of corticosteroids and non-steroidal second-line

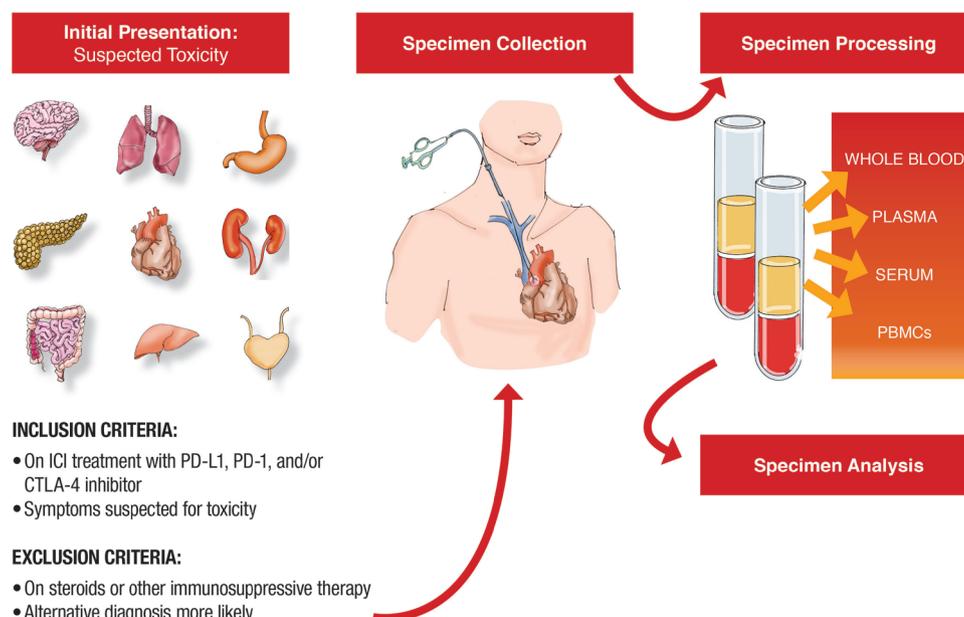


Figure 2 Standard operation procedure for sample collection and processing. CTLA-4, cytotoxic T-lymphocyte antigen-4; PBMCs, peripheral blood mononuclear cells; PD-1, programmed death-1; PD-L1, programmed death-ligand 1.

immunosuppression, ICI discontinuation, and inpatient mortality in the pre-SIC and post-SIC periods.

Statistical analysis

Statistical analyses were performed using Stata, V.15.0 (StataCorp). Descriptive statistics with unpaired t-test for continuous data and Pearson χ^2 test for categorical data were used for comparison of baseline characteristics. Multivariable linear and logistic regressions were used to analyze primary and secondary outcomes. Modeling covariates included age, sex, irAE confirmation status, malignancy, ICI class, primary toxicity type, and presence of multiple toxicities. $P < 0.05$ was considered statistically significant.

RESULTS

From April 2, 2016 through October 3, 2017 (18-month 'pre-SIC' study period), 1169 patients were treated with ICIs at our institution and 127 patients were hospitalized for irAEs. From October 3, 2017 through October 24, 2018 (12-month 'post-SIC' study period), our institution treated 1159 patients with ICIs and 122 patients were hospitalized for irAEs. There were no statistically significant differences in baseline characteristics of patients admitted for irAEs before and after SIC Service implementation (table 1).

The majority of admitted patients both pre-SIC and post-SIC had melanoma, a thoracic malignancy, or a GI malignancy and were treated with either anti-PD-1 monotherapy or combination anti-CTLA-4 and anti-PD-1 therapy. There was a diverse mix of primary toxicity types leading to admission before and after SIC service initiation, with pulmonary, GI, and hepatic irAEs representing the most common toxicities (table 1).

Impact of SIC Service on the primary and secondary outcomes

Critical outcomes data after SIC Service implementation are shown in table 2.

In multivariable modeling, SIC Service implementation was associated with a significant reduction in irAE readmission rates (post-SIC 14.8% vs pre-SIC 25.9%; OR 0.46; 95% CI 0.22 to 0.95; $p = 0.036$) and shorter LOS than pre-SIC readmissions (post-SIC median 6 days vs pre-SIC median 7 days; 95% CI -16.03 to -0.14; $p = 0.046$). We observed a trend toward lower LOS (post-SIC 5 days vs pre-SIC 5.5 days ($p = 0.078$)) but this was not statistically significant.

Overall rates of corticosteroid use, second-line immunosuppression, and ICI discontinuation for irAE, as well as inpatient mortality rates, were not significantly different before and after SIC Service implementation (table 2). A second analysis analyzing the data by first admission only also revealed no significant difference before and after SIC Service implementation in LOS ($p = 0.758$), discharged on steroids ($p = 0.141$), use of non-steroidal immunosuppression ($p = 0.878$), ICI discontinuation for irAE ($p = 0.526$), or inpatient mortality ($p = 0.361$)

indicating first admission acuity was similar among the two groups (online supplemental table 1).

Specimen collection

The sample collection effort began on January 1, 2018. All samples were collected after informed consent from each participant and only when performing clinically indicated diagnostic procedures or at the time of autopsy. The first sample was collected on January 12, 2018. From that date until December 28, 2019, a total of 789 samples were collected from 234 patients with suspected irAEs post-SIC. These samples include 496 blood specimens, 71 bodily fluids (bronchoalveolar lavage $n = 8$, cerebrospinal fluid $n = 9$, synovial fluid $n = 28$, urine $n = 26$) and 222 tissue samples collected during routine care (myocardial, liver, muscle, kidney and GI biopsies, as well as brain, lung and endocrine organ samples from autopsy) (figure 3). Specimens were either processed immediately on arrival to the lab (analysis ongoing), or frozen for future processing and analysis. An illustrative case example is a 53-year-old man with renal cell carcinoma treated with ipilimumab/nivolumab for two cycles who developed presumed ICI-related hepatitis requiring high-dose steroids. The hepatitis resolved and he was re-challenged with nivolumab for eight doses with a course complicated by hypothyroidism, myocarditis with congestive heart failure, and acute kidney injury with significant proteinuria. Nine blood, two urine, and two tissue samples (myocardium, muscle) were collected over the course of his illness (figure 4).

DISCUSSION

In this study, we evaluate the impact of altering a clinical practice model to care for patients with irAEs and creating a clinical-translational research model to study these events. Other services with multidisciplinary toxicity teams include Johns Hopkins University School of Medicine where an electronic referral system for immune-related toxicities was shown to be feasible and helpful to identify patterns of irAEs requiring subspecialist care.¹⁹ Dana-Farber Cancer Institute/Brigham Women's Hospital has initiated a service through which they admitted 194 irAE patients in the first year and found the most common reasons for admission were colitis, hepatitis, and pneumonitis.²⁷ To date, feasibility of these toxicity services has been demonstrated but evidence about the impact pre/post-implementation has not been reported.

Of note, our irAE admission rate of 10%–11% pre/post-SIC intervention is lower than the 41% reported for suspected irAEs and 23% rate for confirmed irAEs in another recent study, conducted at a major academic medical center over a much shorter 7-month period.²⁸ This suggests that although a percentage of irAEs hospitalizations can be avoided, around 10% of

Table 1 Characteristics of patients admitted for irAE before and after SIC Service implementation

Characteristic	Pre-SIC*	Post-SIC†	P value‡
	(n=127 patients)	(n=122 patients)	
Age, mean (SD), years	62.6 (13.9)	64.6 (11.1)	0.216
Female sex	44 (34.7%)	55 (45.1%)	0.093
Cancer type			
Melanoma	48 (37.8%)	31 (25.4%)	0.156
Thoracic	35 (27.6%)	38 (31.2%)	
Gastrointestinal	14 (11.0%)	26 (21.3%)	
Genitourinary	8 (6.3%)	9 (7.4%)	
Hematologic	3 (2.4%)	7 (5.7%)	
Gynecologic	5 (3.9%)	3 (2.5%)	
Head and neck	5 (3.9%)	2 (1.6%)	
Neurologic	3 (2.4%)	4 (3.3%)	
Breast	5 (3.9%)	2 (1.6%)	
Sarcoma	1 (0.8%)	0	
ICI type			
CTLA-4	9 (7.1%)	3 (2.5%)	0.147
PD-1	84 (66.1%)	92 (75.4%)	
PD-L1	8 (6.3%)	10 (8.2%)	
CTLA-4+PD-1	26 (20.5%)	17 (13.9%)	
irAE type			
Allergy	3 (2.4%)	1 (0.8%)	0.311
Cardiac	9 (7.1%)	11 (9.0%)	
Dermatologic	9 (7.1%)	3 (2.5%)	
Endocrine	15 (11.8%)	13 (10.7%)	
Gastrointestinal	28 (22.1%)	20 (16.4%)	
Hepatic	20 (15.8%)	23 (18.9%)	
Hematologic	4 (3.2%)	2 (1.6%)	
Neurologic	10 (7.9%)	14 (11.5%)	
Pulmonary	26 (20.5%)	26 (21.3%)	
Renal	1 (0.8%)	7 (5.7%)	
Rheumatologic	2 (1.6%)	2 (1.6%)	

*Data are presented as number (percentage) of patients, unless otherwise indicated; pre-SIC date range is April 2, 2016–October 2, 2017.

†Data are presented as number (percentage) of patients, unless otherwise indicated; post-SIC date range is October 3, 2017–October 24, 2018.

‡Unpaired t-test for continuous data; Pearson χ^2 test for categorical data.

CTLA-4, cytotoxic T-lymphocyte antigen-4; ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; SIC, Severe Immunotherapy Complications.

patients receiving ICIs develop irAEs that inevitably end in hospitalization.

Importantly, the 6-month irAE readmission rate at our hospital decreased from 25.9% of patients to 14.8% after controlling for age, sex, irAE confirmation status, type of cancer, type of ICI regimen used, and primary toxicity type. Readmissions reduction is critically important as it is an opportunity to improve patient care and satisfaction, improve quality, and decrease healthcare costs. One potential explanation for the decrease in readmissions

may have been the comprehensive inpatient care by SIC experts and consultants, the streamlined transition on discharge to outpatient care, and the network of outpatient subspecialists who provide significant continuity.

In addition, the post-SIC Service LOS for irAE readmissions also decreased from 7 to 6 days in comparison with the pre-SIC study period, a key finding which has implications for patients and healthcare systems. These findings are particularly important as readmission rates are commonly used measures for quality of care; it is estimated

Table 2 Impact of SIC Service implementation on key outcomes—logistic regressions

Outcome	Pre-SIC*	Post-SIC†	Coefficient/OR (95% CI)‡	P value
	(n=166 admits)	(n=149 admits)		
Length of stay, median (IQR), days	5.5 (3–11)	5 (3–9)	−1.7 (−3.56 to 0.19)§	0.078
Discharged on corticosteroids¶	121 (75.6%)	96 (69.1%)	0.60 (0.33 to 1.10)**	0.101
Use of non-steroidal immunosuppression	24 (14.5%)	18 (12.1%)	0.87 (0.43 to 1.77)**	0.702
ICI discontinuation for irAE††	74 (66.1%)	61 (67.0%)	1.04 (0.55 to 1.98)**	0.897
Died during irAE admission	11 (6.6%)	13 (8.7%)	1.46 (0.60 to 3.55)**	0.398
irAE readmission	43 (25.9)	22 (14.8)	0.46 (0.22 to 0.95)‡‡	0.036
Length of stay of irAE readmission, median (IQR), days	7 (3–16)	6 (3–10)	−8.08 (−16.03 to 0.14)§	0.046

Bold values are statistically significant,

*Data are presented as number (percentage) of admissions, unless otherwise indicated; pre-SIC date range is April 2, 2016–October 2, 2017.

†Data are presented as number (percentage) of admissions, unless otherwise indicated; post-SIC date range is October 3, 2017–October 24, 2018.

‡Data are presented as coefficient (95% CI) for linear regressions (continuous variables) and OR (95% CI) for logistic regressions (categorical variables).

§Multivariable linear regression with covariates: age, sex, irAE confirmation status, malignancy, ICI class and primary toxicity type.

¶Excludes patients with thyroid toxicities or diabetes mellitus (given steroids are not indicated) as the irAE. Pre-SIC n=160; post-SIC n=139.

**Multivariable logistic regression with covariates: age, sex, irAE confirmation status, malignancy, ICI class, primary toxicity type and presence of multiple toxicities.

††Excludes patients with endocrine toxicities (given ICI discontinuation is not indicated) as well as patients who previously discontinued ICI prior to admission or discontinued ICI for any non-irAE reason (disease progression). Pre-SIC n=112; post-SIC n=91.

‡‡Multivariable logistic regression with covariates: age, sex, irAE confirmation status, malignancy, ICI class, primary toxicity type, presence of multiple toxicities and ICI discontinuation for toxicity.

ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; SIC, Severe Immunotherapy Complications.

that Medicare spends \$17 billion a year on avoidable readmissions, and in recent years, the US Hospital Readmissions Reduction Program has begun penalizing hospitals with high 30-day readmission rates.²⁹ Thus, if a dedicated SIC Service can significantly improve these quality of care

measures, it could result in meaningful gains for both patients and hospitals.

After instituting the SIC Service, the mortality rate for patients hospitalized for irAEs did not significantly change. Our pre-SIC mortality rate of 6.6%

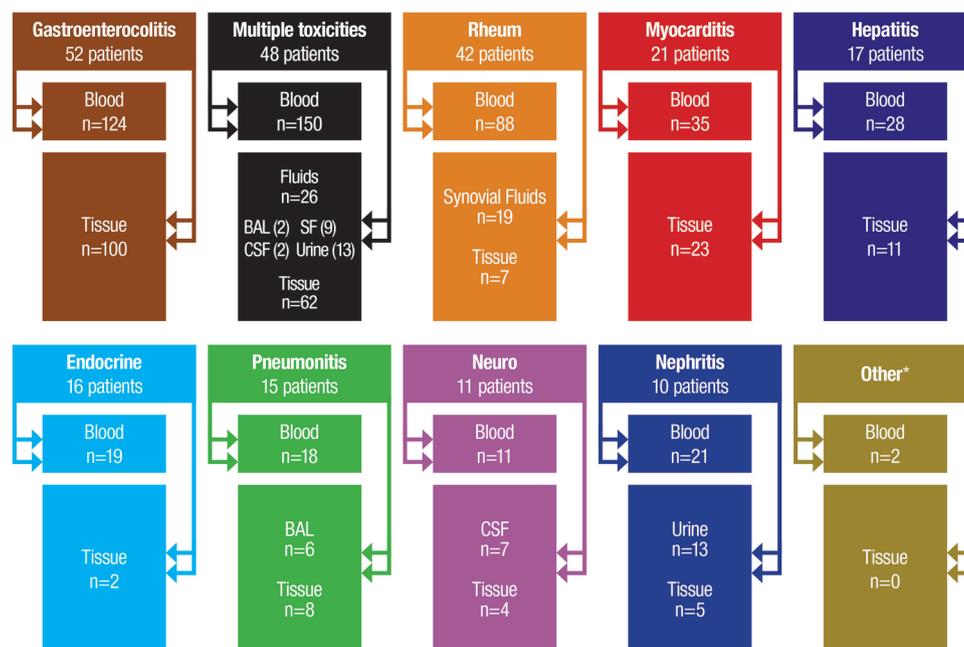


Figure 3 Number of patient samples (blood, bodily fluids, tissues) collected. *Other=one case of hematological toxicity and one case of pancreatitis. BAL, bronchoalveolar lavage; CSF, cerebrospinal fluid.

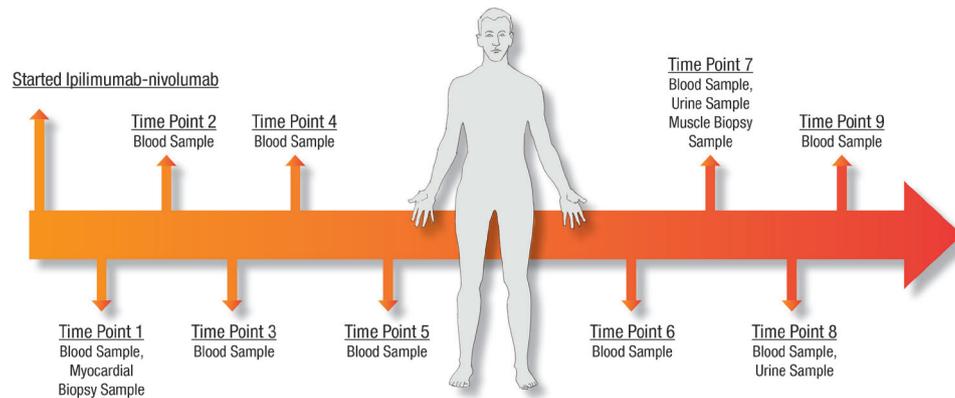


Figure 4 Serial blood and tissue samples in an irAE patient with multiple toxicities. irAE, immune-related adverse event.

(over 12 months) and post-SIC mortality rate of 8.7% (over 18 months) are similar to the 7.3% mortality rate reported in a 7-month irAE study conducted by another major academic medical center where clinical outcomes on patients hospitalized for irAEs were also analyzed.²⁸ Further steps to decrease inpatient mortality relating to irAEs likely await new developments in the treatment for toxicity.

Importantly, the data presented indicate SIC Service implementation was not associated with any negative outcomes despite integrating research blood and tissue collection into routine care. There were numerous samples collected but no sign of detrimental impact on clinical care—no difference in LOS, inpatient mortality, or readmission rate. Therefore, this study demonstrates safety and feasibility of collecting a wide range of biological samples from patients with irAE on an inpatient service. These specimens are being used for an ongoing effort to investigate predictive blood biomarkers for irAEs and identify mechanisms of irAE development. In this study, 789 blood and tissue samples were collected from 234 patients who developed irAEs in the first 2 years of the service. We found that the effort required to obtain timely patient consent for study participation and to collect the samples prior to steroids was considerable. Staff had to overcome a number of challenges including (1) seriously ill patients spread over 15 different floors of the hospital with staff often unfamiliar with the protocol; (2) patients who were often absent from their rooms to undergo imaging studies or procedures; (3) language barriers; (4) difficulty in obtaining blood; (5) delays and frequent rescheduling of inpatient procedures; (6) insufficient tissue quantity of specimen remaining for research after the necessary clinical samples were obtained; and (7) access to rapid and adequate processing in a timely fashion. Thus, if the oncology research community is to respond to the call for biomarker-based studies of irAE mechanisms and identification of potential biomarkers to detect patients at high risk of irAE, funding along with dedicated and coordinated services, or a central infrastructure, will likely be needed in order to scale efforts sufficiently.^{5,30}

In order to propel this type of translational discovery, it will take a multi-institutional effort to pool samples in order to (1) uncover set of predictive factors for irAEs; (2) understand early mechanisms driving irAEs; (3) identify novel drug targets; and (4) develop better therapeutic strategies. This study is the first to report this type of effort is feasible and safe, and can be embedded in clinical care.

This study has several important limitations. First, it describes observations at a single institution and therefore results may not be representative of other institutions. Second, because our institution is an academic medical center housed within a general hospital, we were able to recruit numerous subspecialists focused on autoimmunity with an interest in irAEs across the spectrum; this may limit the study's generalizability. Third, to ensure accuracy, in this study we only included data from patients who received both ICI therapy and irAE care at our institution; thus, our results do not reflect the experience of patients transferred to our hospital for irAE care, who tend to be in more critical condition, or patients who were treated with ICIs at our institution but hospitalized for irAEs elsewhere. Finally, a general improvement in knowledge and experience over time in managing irAEs may have led to the observed differences in the pre-SIC and post-SIC groups. During the time period of this study, new sets of guidelines from the American Society of Clinical Oncology and NCCN emerged. Therefore, we cannot exclude that increased irAE awareness and management skills among care providers, independent of the SIC service, affected the readmission rate and LOS.

In conclusion, this study is, to the best of our knowledge, the first to report that establishing a highly subspecialized care team focused on irAEs can be associated with improved clinical outcomes for patients receiving ICI therapy, while also building the infrastructure needed to drive future clinical research on ICI toxicities. Such care teams are likely to serve as a model and may play an essential role in improving irAE care: defining phenotypes, identifying diagnostics for early detection, developing biomarkers to assess irAE severity, and generating preliminary data to

guide next-generation clinical trials for the treatment of irAEs. In addition, maintaining a central registry of patients, fostering a collegial group dynamic, having regular meetings, and a focus on collaboration across subspecialties and oncology have the potential to foster that future discovery. These teams will also play a key role in bringing these advances back to the bedside to benefit patients.

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Contributors LZ and GEM devised the project idea, acquired and analyzed data, performed statistical analysis, and wrote the manuscript. MJM, JC, SD, LP, GMB, DJ, MD, MFT, ATF, MR, ACG, STC, DO, BDM, MN, MK, SS, RKL, MES, TGN, DZ, JRF, AB, RS, SB, YRS and A-CV provided critical intellectual input to study design and analysis and edited the manuscript. KLR created the registry of immunotherapy toxicity cases and samples, devised the project idea, designed the study, and supervised the statistical analysis and manuscript development.

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