Article

Light Chain Disorders Associated with COVID-19 Vaccines

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Abstract: Serum free light chain (sFLC) elevation following SARS-CoV-2/COVID-19 infection/illness and COVID-19 mRNA vaccination may indicate adverse immunological responses, such as clonal proliferation or inflammation.[1,2] To evaluate the use of sFLC measurements, the Vaccine Adverse Event Reporting System (VAERS), maintained by the Centers for Disease Control and Prevention and the Food and Drug Administration, was searched for sFLC abnormalities following COVID-19 vaccination. Seventy-five (75) unique cases were identified that included quantitative sFLC measurement or diagnosis of free light chain disorders following at least one injection of COVID-19 vaccine. Twenty-five cases (33%) had complete quantitative data for serum kappa (κ) and lambda (λ) and kappa/lambda ratio (sFLCR), and 50 cases (67%) had incomplete quantitative sFLC data but carried a diagnosis of sFLC disorder with supporting documentation. Quantitative and qualitative data were extracted and analyzed using Grok 3 (xAI). Severity was classified as hospitalization (H), life-threatening (LT), permanent disability (PD), or death (D), with correlations to vaccine type (Pfizer, Moderna, mixed), number of doses (1–5), and time to onset (0–518 days). Fifty of 75 cases (67%) were severe. A high κ/λ ratio (sFLCR) (>1.65) was associated with neoplastic and paraneoplastic conditions. Ratios (sFLCR) ≤ 1.65 ≥ 0.26 were associated with inflammation. All three cases with low ratios (<0.26) had lambda dominance and involved neoplasia (multiple myeloma x 2, lymphoma x1). Organ system analysis identified renal (36%), neurological (16%), hematological (17%), and IgA-related (17%) manifestations. Renal and hematological cases tended to occur early (renal average = 12.5 days, hematologic average = 36 days) with lower doses (renal = 1.86, hematologic = 2.46) and neurological cases later (average 127.5 days) with higher doses (average = 2.92). sFLC measurements should be further evaluated as a tool to diagnose and monitor neoplastic and inflammatory disease activity following COVID-19 vaccination.

Keywords: serum free light chains (sFLCs); kappa (sFLCκ); lambda (sFLCλ); κ/λ ratio (sFLCR); COVID-19 mRNA vaccines; vaccine adverse event reporting system (VAERS); immunological dysregulation; multiple myeloma (MM); renal disorders; clonal severity; organ systems; dose-dependent risk; chronic inflammation

1. Introduction

sFLC Biology

In 1847 Henry Bence Jones reported finding a novel protein in the urine of a patient with *mollities ossium*, a fatal condition characterized by softening and deformities of bone.[3,4] Early in the 20th century the proteins identified by Bence Jones were determined to be produced by neoplastic plasma cells.[5] In the early 21st century, serum free light chain (sFLC) measurements replaced urinary Bence Jones protein analysis for screening and monitoring multiple myeloma.

Produced by B lymphocytes, immunoglobulins consist of two heavy and two light polypeptide chains. The heavy chains come in IgG, IgM, IgA, IgD, and IgE varieties. The light chains have two forms, kappa (κ) and lambda (λ). Light chains are produced in greater quantities than heavy chains

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with kappa produced in quantities double that of lambda chains. The range of normal values for serum kappa chains is 3.3-19.4 mg/L and 5.7-26.6 mg/L for lambda, with a normal ratio of 0.26-1.65.[5]

Clinical Relevance: Neoplasia versus Inflammation

Serum free light chain determinations have had an expanding role in medical diagnostics and disease management for both neoplastic and more recently inflammatory disorders. Jenner compiled data from multiple sources to identify a "broad spectrum" of neoplastic monoclonal plasma cell variants including κ Light Chain Multiple Myeloma (κLCMM), λ Light Chain Multiple Myeloma (λLCMM), Non Secretory Multiple Myeloma (NSMM), Intact Immunoglobulin Multiple Myeloma (IIMM), and AL Amyloidosis (ALM). Numerical data for κ, λ, and sFLCR were compiled for six conditions that were presented as a dot-plot.[5] (Supplement Jenner Figure 1)

Cases with sFLCR (κ/λ ratio) in the range < 0.26 or >1.65 are associated with hematopoietic neoplasms and paraneoplastic conditions. The sFLC abnormalities have been studied in the following plasma cell neoplastic or paraneoplastic conditions (Table 1) which is a small sample of the 39 B-cell and 23 T-cell neoplasms recognized by the World Health Organization.[6]

Table 1. Neoplastic and paraneoplastic conditions potentially having out of reference values for sFLCR.

Classification of Plasma Cell Neoplasms and Paraneoplastic Conditions [7–15]
1. Non-IgM MGUS
2. Smoldering myeloma
3. Multiple myeloma
4. Solitary bone plasmacytoma
5. Solitary extraosseous plasmacytoma
6. Immunoglobulin light chain amyloidosis
7. Localized AL amyloidosis
8. Waldenström macroglobulinemia
9. Light chain deposition disease (LCDD)
10. POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M-protein, skin changes)

Gudowska-Sawczuk and Mroczko performed a comprehensive search of the literature up to 2023 in which they identified FLCs as biomarkers of inflammatory diseases including SARS-CoV-2 infection as well as monoclonal gammopathies, Table 2.[16]

Table 2. Conditions associated with Abnormal sFLC.

Monoclonal Gammopathies	Diabetes
Multiple sclerosis	Cardiovascular disease
SARS-CoV-2 infection	Rheumatoid arthritis
HCV	Sjogren's syndrome
HBV	SLE
HIV	Lung cancer
Lyme Disease	Breast cancer
Tick-born encephalitis	Bowel Disease

HCV = Hepatitis C Virus, HBV = Hepatitis B Virus, HIV = Human Immunodeficiency Virus, SLE = Systemic Lupus Erythematosus.

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Use of sFLCκ, sFLCλ and sFLCR measurement continues to expand as a diagnostic and management tool that gives insight about function of terminally differentiated B-cells also known as plasma cells. These measurements provide some insight into the functioning of cells that are active in responding to inflammatory conditions and a growing array of neoplastic and pre or para neoplastic conditions. Recent studies highlight the diagnostic utility of sFLC levels in various conditions, including

CNS disorders, type 2 diabetes, cardiac disorders, renal disorders, protein deposition in multiple organs, and following COVID-19 vaccination.

- Hegen, H., et al., reported on cerebrospinal fluid kappa free light chains as biomarker in multiple sclerosis from diagnosis to prediction of disease activity.[17]
- Demortiere, et al. found kappa FLC index in patients with inaugural optic neuritis was useful to sort out multiple sclerosis (MS), myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) and neuromyelitis spectrum disorder (NMOSD).[18]
- Bracco et al. found the presence of FLC in cerebrospinal fluid of multiple sclerosis patients implicated a recent immunological stimulation leading to increased synthesis of FLC within the central nervous system.[19]
- Matsumori et al. found that sFLCR was a "…more specific and sensitive for the diagnosis of T2D than HbA1c, and thus represents a potentially promising biomarker of inflammation."[20]
- Basile, et al. found sFLCR > 0.63 was associated with left ventricular ejection fraction improvement in a small series of patients with NSTEMI, STEMI and stable angina at one year follow up.[21]
- Nakao, H. reported an increase in IgA nephropathy following COVID-19 mRNA vaccination.[22]
- Park and Kwon pointed out the role of monoclonal FLC in producing kidney damage in Monoclonal Gammopathy of Renal Significance (MGRS) without multiple myeloma or other forms of neoplasia.[23]
- Martins, et al. reported on 23 cases of non-myeloma light chain cast nephropathy (non MM-LCCN) pointing out that malignancy develops later in 43% of cases.[24]
- Lan, et al. presented a case of light chain proximal tubulopathy (LCPT) and light chain cast nephropathy (LCCN) in a 49 year-old patient with acute kidney injury associated with of lambda light chain multiple myeloma (LCMM).[25]
- Cassano, et al. reported on light chain deposition disease (LCDD) in which non-amyloid monoclonal light chains are deposited in different organs particularly kidney where monoclonal immunoglobulins are deposited in vascular basement membranes, glomerular basement membranes and tubular basement membranes in patients with plasma cell dyscrasias but also monoclonal gammopathy of unknown significance (MGUS).[26]
- Gudowska-Sawczuk, et al. found COVID-19 vaccinated subjects had higher sFLC levels than COVID-19 patients and unvaccinated controls.[2]

  Gudowska-Sawczuk, et al. conclude,

  … abnormal levels of κ and λ FLCs, as well as the ratio of κ:λ, are usually the result of disturbances in the synthesis of immunoglobulins as an effect of overactive inflammatory reactions. Therefore, it seems that κ and λ FLCs may be significant diagnostic and prognostic biomarkers of selected diseases. Moreover, the inhibition of FLCs appears to be a promising therapeutical target for the treatment of various disorders where inflammation plays an important role in the development or progression of the disease.[2]

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The desired outcome from study of free light chain (sFLC) is identification of a biomarker of diseases that affect the immune system with more specificity and sensitivity than the common indicators of inflammation, the erythrocyte sedimentation rate (ESR) and C reactive protein (CRP), with the additional value in diagnosis and management of neoplasms of terminally differentiated B-cells.

This article will examine sFLC patterns (κ, λ, and sFLCR) following injection of Pfizer/BioNTech's BNT162b2, Moderna's mRNA1273 and JNJ/Janssen's Jcovden using cases drawn from the VAERS database.

2. Materials and Methods

The Vaccine Adverse Event Reporting System (VAERS), maintained by the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA), catalogs adverse events following COVID-19 vaccination. VAERS cases are voluntarily submitted by individuals, including medical professionals, who suspect a possible causal relationship between the reported conditions and administered COVID-19 vaccines.

Search terms included all FLC-related identifiers and free-text field searches for FLC reporting in Adverse Event Descriptions and Lab Data sections of VAERS reports. Specific conditions searched included multiple organ system related diagnoses such as renal disorders, CNS disorders, hematological disorders, and cardiac disorders. A master spreadsheet was constructed and analyzed using Grok 3 (xAI), an AI tool designed for data analysis, proofing and preparation of tables.

This study examines 75 unique VAERS cases in two cohorts; 25 Complete, 50 Incomplete, reporting free light chain (FLC) abnormalities potentially associated with COVID-19 mRNA vaccines, with data updated as of March 17, 2025. Cases were categorized as "Complete" (quantitative κ/λ/sFLCR data) or "Incomplete" (qualitative or partial κ/λ/sFLCR data). Severity was assessed for hospitalization (H), life-threatening events (LT), permanent disability (PD), and death (D). Time to onset, vaccine type, number of doses, organ system involvement, and biopsy cases were examined

The following framework derived from Jenner and Gudowska-Sawczuk, et al., was used to analyze the quantitative VAERS data. Normal versus Abnormal sFLCR was used as an ordering principle to analyze data with subset analysis according to κ and/or λ levels.

Table 3. sFLCR: Inflammation or Neoplasm.

Type	sFLCR	sFLC
Inflammatory	0.26–1.65	κ, λ, κ & λ
Neoplastic	<0.26 or >1.65	κ, λ, κ & λ

3. Results (See Supplement Tables S1, S2, S3, S4, S5)

Quantitative Cases n = 25 (Supplement Tables S1A-F)

Severe adverse events occurred in 68% (17/25) of these cases. Hospitalization (H) was present in 73% of the 17 severe cases, Life Threatening (LT) in 24%, Permanent Disability (PD) in 16%, and Death (D) in 4%. Pfizer was the most common vaccine type (60%, 15/25). Time to onset was less than or equal to 7 day in 39% of these cases. Average values for κ/λ/sFLCR are 95/331/9.46, well above normal values for all three. (Table 4)

Table 4. k/l/sFLCR data for Quantitative Cases n = 25.

	κ	λ	sFLCR
Avg	94.6	330.5	9.46
Min	4.27	0.44	0.01

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Max	338	5975	165.61

Table S1F presents data for two cases in which the sFLCR was elevated, kappa, was normal and lambda was < 0.26 suggesting immunosuppression and not proliferation. The denominator for the neoplasia calculations was therefore reduced by two to 23. Neoplasia was identified in 57% of the 23 cases.

Table 5. Neoplasia in 57% (13 of 23).

Condition	Cases	% of Total
Leukemia	1	4%
Plasmacytoma	1	4%
Monoclonal Gammopathy	3	13%
Multiple Myeloma	4	17%
Lymphoma	4	17%
Total	13	57%

Eighty-five percent (85%) of cases with sFLCR (κ/λ) > 1.65 or < 0.26 had neoplastic/paraneoplastic conditions compared with 30% of cases with sFLCR ≥ 0.26 and ≤ 1.65.

Table 6. Neoplasia by Normal versus Abnormal k/l Ratio.

	Neoplastic
Normal sFLCR 43% of cases (10/23)	30% (3/10)
Abnormal sFLCR 57% of cases (13/23)	85% (11/13)

This difference is statistically significant using Fisher's Exact Test for $p < 0.05$ (0.013).[27] This cohort analysis affirms the use of sFLCR as an indicator for neoplastic monoclonal gammopathy if the ratio exceeds 1.65 or is less than 0.26. It has been reported that a ratio over 100 indicates multiple myeloma.[8,13] This cohort had one case with a ratio > 100 that was a myeloma case. However, Cases 60 (lymphoma) and 63 (monoclonal gammopathy/plasmacytoma) had normal ratios.

For cases in which the ratio ≤1.65 but in which κ and/or λ exceed the 95 percentile range serial sFLC determinations should be considered for serial FLC monitoring. Malignant transformation is reported to occur in up to 30% over 20 years for non IgM monoclonal gammopathy of unknown significance (MGUS) patients with two risk factors, elevated ratio and high serum monoclonal protein greater than or equal to 1.5 g per deciliter.[8,13] Serial sFLC determinations may also be a useful indicator of disease activity in cases of inflammatory disease as well as neoplastic diseases.[2,7–26]

Summary and Clinical Analysis of Supplement Table S2 Qualitative Cases n = 50

Supplement Table S2 encompasses 50 cases with incomplete quantitative data but sufficient documentation to confirm sFLC disorders post-vaccination. The data reveal that 68% (34/50) of these cases are severe, with a notable prevalence of IgA-related disorders (16%, 8/50) and a majority involving two doses (52%, 26/50). This suggests broader immune activation, possibly involving mucosal immunity, compared to the complete data cohort.

Neoplasia (multiple myeloma, monoclonal gammopathy, plasmacytoma, lymphoma, and leukemia) was identified in 31% of cases. This is in contrast to 52% of cases in the quantitative cohort discussed above. (Supplement Table S1).

Combined

Table 7. Demographics, Vaccine Type, Severity, and Neoplasia prevalence for 75 VAERS Cases (Supplement Table S4).

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Category	Summary
Age	Mean: ~60 years (n=65) Range: 19–87 years Unknown: 10 cases (13.3%)
Sex	Male: 57% (39/68) Female: 40% (27/68) Prefer Not to Say: 1% (1/75) Unknown: 4% (3/75)
Vaccine Type	Pfizer: 60% (39/65) Moderna: 28% (18/65) Pfizer/Moderna (mixed): 9% (6/65) Unknown: 10% (7/75) Janssen: 0%
Severity	Severe: 67% (50/75) - Hospitalization: 57% (43/75) - Life-Threatening: 13% (10/75) - Permanent Disability: 11% (8/75) - Death: 5% (3/75) Non-Severe: 33% (25/75)
Presence of Neoplasia	Yes: 53.3% (40/75) No: 46.7% (35/75)

The average age was 60 years with male dominance. Pfizer was the vaccine most commonly used. Sixty-severe percent of adverse events were severe. Neoplasia was identified in 40 cases. (Table Supplement Table S4). Four cases had preexisting multiple myeloma (Quantitative Cohort 1 case, Qualitative Cohort 3 cases). There was one case of preexisting chronic myelogenous leukemia and one case of pre-existing light chain disease.

Table 8 Death Case Analysis

Table 8. Deaths.

	LC #18	LC #19	LC #57
Age and Sex	71-year-old female	78-year-old female	62-year-old male
Vaccine Type	Pfizer	Pfizer	Pfizer
Number of Doses	2	2	1
Time to Onset	215 days	254 days	2 days
Diagnoses	Plasma cell dyscrasia, ARDS, COVID-19 pneumonia, renal amyloidosis/AKI	AKI, CKD, anemia, Stevens-Johnson syndrome	AKI, found dead, anemia, small M spike (IgM lambda)

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Light Chain Status	Elevated kappa and lambda chains	Elevated IgG kappa	kappa 68.55 mg/L, Lambda 35.39 mg/L, Ratio 1.94
Pre-existing Illness	None documented	T2DM, CAD (NSTEMI, DES 2015), hypertension, hyperlipidemia, depression	Substance abuse, renal injury

The Pfizer vaccine was associated with deaths in the cases identified as LC 18, LC 19, and LC 57. No other vaccines were associated with deaths in this specific set of cases. Median time to onset was 14 days with mean of 40 days range (0-518). Nothing in the data recorded in VAERS causally links deaths with BNT162b2. Case LC#57 has close temporal association with the vaccine, 2 days, but other potential causes of death were present.

Organ-Specific Analysis (Supplement Tables S3, Complete list of diagnoses S4)

Table 9. Organ Specific Findings.

Category	**Renal**	**Hematological**	**Neurological**	**Cardiac**
Summary Statistics	28/75 (37%); 24/50 Severe (47%)	13/75 (17%); 10/50 Severe (20%)	12/75 (16%); 10/50 Severe (20%)	2/75 (3%); 2/50 Severe (4%)
Diagnoses	Nephrotic syndrome, anti-GBM nephritis, amyloidosis	Multiple Myeloma (MM), Monoclonal Gammopathy of Undetermined Significance (MGUS)	Guillain-Barré	Myocarditis, Cerebrovascular Accident (CVA)
Symptoms	Proteinuria (15), hematuria (11), AKI (8)	Anemia (10), thrombocytopenia (3)	Gait disturbance (5), neuropathy (3)	Myocarditis, CVA

Metric	**Statistical Test Results [29]**	**Significant Pairwise Comparisons (Adjusted $p < 0.05$)**
Number of Doses	Kruskal-Wallis p=0.0198, indicating significant differences among renal, hematologic, and neurologic systems.	Neurologic (median=3, mean=2.92) vs. Renal (median=2, mean=1.86), p=0.015. No significant differences for Renal vs. Hematologic (median=2, mean=2.46) or Hematologic vs. Neurologic (p>0.05).
Time to Onset	Kruskal-Wallis p=0.0403, indicating significant differences among renal, hematologic, and neurologic systems.	Neurologic (median=127.5 days, mean=140.90) vs. Renal (median=12.5 days, mean=43.55), p=0.033. No significant differences for Renal vs. Hematologic (median=36 days, mean=99.67) or Hematologic vs. Neurologic (p>0.05).

Primary renal involvement was identified in over a third of the cases followed by hematologic and neurologic disease in a sixth of cases for each. Renal and hematological systems had significantly shorter onset times ($p < 0.05$) with significantly fewer doses $p < 0.05$).

Table 10. Biopsy Cases: (See Supplement Table S5, S6) 28% (21/75).

Category	**Summary**

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Biopsy Site	Renal (Kidney): 13 cases (62%) – IgA nephropathy (5), glomerulonephritis (4), nephrotic syndrome (2), light chain nephropathy (1). Hematologic (Bone Marrow/Bone): 10 cases (48%) – myeloma (3), MGUS (2), light chain disease (1), lymphoma (1). Other : 1 case (4.8%, UGI, negative). Multi-Site : 4 cases (20% kidney + bone marrow).
Vaccine Type	Pfizer: 14 cases (67%) – 8 renal (e.g., IgA nephropathy), 3 neoplastic (e.g., myeloma, MGUS), 1 autoimmune. Moderna: 7 cases (33%) – 5 neoplastic (e.g., myeloma, MGUS), 2 renal (e.g., IgA nephropathy).
Severity Level	Hospitalization: 7 cases (33%) – renal (e.g., IgA nephropathy), systemic complications. Life-Threatening: 4 cases (19%) – myeloma, lymphoma, light chain nephropathy. Permanent Disability: 4 cases (19%) – myeloma, nephrotic syndrome, MGUS. Unspecified: 5 cases (24%). Emergency Room: 1 case (4.8%). Note: >71% severe outcomes.
Presence of Neoplasm	Present: 8 cases (38%) – plasma cell myeloma (3), MGUS (2), light chain disease (1), lymphoma (1), monoclonal gammopathy (1). FLC Association: All show elevated kappa/lambda or abnormal ratios. Vaccine: Moderna (5/8), Pfizer (3/8) Severity: Includes life-threatening, permanent disability, hospitalization. Note: Tied to bone marrow involvement.

Renal and hematologic systems were the organs most frequently biopsied (61% and 48%). Pfizer was more common in renal disorders and Moderna to neoplasms (71% of Moderna cases). Over 71% of biopsy cases were rated as severe. Neoplasms (38%) are strongly sFLC-associated, with Moderna showing higher neoplastic proportion.

4. Discussion

COVID-19, COVID-19 Vaccines and sFLC Patterns

Using a technique called WBC differential fluorescence (WDF) Malecka-Gieldowska, et al., found antibody synthesizing lymphocytes in much greater concentration in 45 COVID-19 ICU patients than 45 non-COVID-19 ICU patients.

Malecka-Gieldowska, et al. found a 3-fold increase in synthesis of kappa light chains in SARS-Cov-2 infected ICU cases compared with non-infected ICU cases.[1] Further, elevated kappa light chains differentiated COVID-19 ICU patients from non-ICU COVID-19 patients. COVID-ICU patients were also found to have neutrophilia, lymphopenia and elevated neutrophil to lymphocyte ratios (NLR). Malecka-Gieldowska, et al. observed,

The differences between the concentrations of kappa and lambda chains in patients from the COVID ICU, COVID non-ICU and non-COVID ICU groups prove that infection with SARS-CoC-2 stimulates FLC synthesis in the human body, most importantly in the group of ICU patients hospitalized in the intensive care unit.[1]

They concluded that, "… monitoring of FLC concentration in COVID-19 convalescents might be essential for early detection of possible development of lymphoproliferative disorders."

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Gudowska-Sawczuk, et al. extended the analysis of free light chains comparing free light chain data in COVID-19 patients with vaccinated controls and unvaccinated controls.[2] Gudowska-Sawczuk, et al. found, "…serum concentrations were significantly higher in COVID-19 and vaccinated controls in comparison to non-vaccinated controls ($p < 0.001$ for both)." Thus, the COVID-19 vaccines induce sFLC synthesis similar to SAR-CoV-2.

Table 11 below compares κFLC, λFLC, and sFLCR across six groups: COVID-19 Vaccine Cases (derived from Supplement Table 1 of this study, n=25), COVID-19 ICU Patients, COVID-19 non-ICU Patients, Vaccinated Controls, Mild COVID-19 Patients, and Non-COVID Controls.[1,2] This comparison aims to elucidate the extent of FLC elevation in vaccine-related cases relative to COVID-19 infection and control groups, supporting the hypothesis of vaccine-induced immune dysregulation.

Table 11. Comparison with sFLC for COVID-19 ICU, COVID-19 non-ICU, Vaccinated Controls and Non Vaccinated Controls. Elevated values are in red.

Group	κFLC (mg/L)	λFLC (mg/L)	κ/λ Ratio
COVID-19 Vaccine N = 25	94.6 (7.05–300)	331 (3.49–7176)	9.46 (0.09–165.61)
COVID-19 ICU[1] n = 45	47.03 (43.52–64.76)	34.71 (30.66–47.23)	1.34 (1.20–1.52)
COVID-19 non-ICU[1] n = 43	24.62 (21.22–36.45)	25.83 (19.26–28.38)	1.27 (1.06–1.35)
Vaccinated Controls[2] n = 20	17.83 ± 3.03 (12.10–23.70)	13.22 ± 3.87 (9.24–22.00)	1.40 ± 0.24 (0.88–1.77)
Mild COVID-19[2] n = 80, (67 vaccinated)	16.76 ± 5.51 (5.25-42.50)	16.38 ± 6.17 (6.32-36.50)	1.10 ± 0.28 (0.44-1.94)
Non-Vaccinated Controls[1] n = 20	10.25 ± 2.13 (6.28–15.04)	10.26 ± 2.76 (6.84–18.89)	1.03 ± 0.22 (0.51–1.41)

Table 11 data highlights a stark contrast in FLC patterns. COVID-19 Vaccine Cases exhibit the highest mean κFLC (94.6 mg/L) and λFLC (331 mg/L), with a mean κ:λ ratio of 9.46, far exceeding the normal range (0.26–1.65). VAERS vaccine cases have values > COVID-19 ICU Cases > COVID-19 non ICU Cases > Vaccinated controls > Mild COVID-19 cases > Non-Vaccine Controls. This aligns with Table 1's finding that 60% of Complete cases (15/25) have high ratios (>1.65), with higher neoplastic prevalence. These cases rate higher in severe outcomes like permanent disability (PD) or hospitalization (H).

In contrast, normal ratios (≤1.65) in COVID-19 Vaccine Cases and other groups suggest polyclonal inflammation, as seen in chronic inflammatory states. Table 11 shows ICU (κFLC: 47.03 mg/L, λFLC: 34.71 mg/L) and non-ICU patients (κFLC: 24.62 mg/L, λFLC: 25.83 mg/L) with elevated FLCs compared to controls, but their normal ratios indicate inflammation rather than clonal proliferation, consistent with COVID-19-driven immune activation. Low ratios (<0.26) in Vaccine Cases point to lambda-driven clonal pathology.

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It must be noted that selection bias for abnormal values is present in the current 25 COVID-19 vaccine cases that was not present in the two published studies. Additionally, patients in the COVID-19 Vaccine cohort had significant co-morbidities and severity of disease that was not identified in the two published studies. Statistical comparisons with the two published studies were not performed for this reason.

The out of normal reference ranges for sFLCR was affirmed as a statistically significant indicator of neoplasia in the cohort with quantitative sFLC data 85% prevalence in the ≤ 0.26 and ≥ 1.65 subgroup compared with 20% in those with normal values.

Organ Specific Findings

Inflammatory conditions, proteinopathy and neoplasia characterize diseases associated with COVID-19 vaccines with renal involvement twice as prevalent as hematologic or neurologic. Renal and hematological conditions had shorter onset times and with fewer doses. This finding may be related to the fact that the kidneys rapidly process free light chains and if present in sufficient quantity both glomerular and interstitial disease may result from excess free light chain production. Detailed data from longitudinal observation should help sort out the various contributing factors.

IgA Related Disorders

FLC elevations in Vaccine Cases correlate with IgA-related disorders (17%, 13/75), as seen in (e.g., File #75, PD, IgA Lambda band, κFLC 130 mg/L). The association between IgA nephropathy and COVID-19 vaccines was reported by Nakao, Hiroka, et al. based on safety signals from the Japanese Adverse Event Drug Reporting System (JADER) which had 30 cases of IgAN. Of 16 cases with onset data 11 occurred within 2 days or less following the vaccination.[22].

Implications for Vaccine Safety

The findings in Table 11, combined with Table S3's severity analysis (67% severe cases), highlight FLC abnormalities as a potential marker for vaccine-related adverse events. The gradient of FLC elevation—highest in Vaccine Cases, followed by ICU, non-ICU, Vaccinated Controls, and Non-COVID Controls—implies increasing severity of immune challenge from infection from SARS-CoV-2 to injection with COVID-19 vaccines.

Limitations

Bias is a concern due to small group size with reduced statistical power, absent longitudinal data, and incomplete data sets. Selection of cases from VAERS was based on abnormal values for κ/λ/sFLCR. Cases in the two literature studies were not so selected and many or most values in these studies were within normal limits. These studies looked at differences between cohorts rather than out of range high values for the three sFLC variables and out of range low values for sFLCR. VAERS is known to under report prevalence, potentially significantly making application to population data problematic.[28]

The findings and conclusions from this study are intended for hypothesis generation, not definitive statements on free light chain disorders causally related to COVID-19 vaccines. The VAERS cases are made complex by voluntary and patchy reporting, multiple co-morbidities and absent follow up. Definitive observations require additional data from future datasets. Causation is not proven with VAERS studies.

5. Conclusions

Although not proven statistically by this analysis, Pfizer vaccines ranked first in severity, including all three deaths, Moderna (21.6%) had acute life-threatening events in 36.4%, and multiple doses were associated with chronic conditions (H: 100% at 4+ doses, Table S3). Renal (37% of cases)

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and hematological disorders (17% of cases) occur earlier with fewer doses, while neurological (16% of cases) disorders have later onset with more doses. ($p < 0.05$)

High FLC ratios (>1.65) were found in 60% of Complete cases and were associated with neoplasia/para neoplasia in 85% of cases while normal ratios ($\leq 1.65 \geq 0.26$) with elevation sFLCκ and or sFLCλ reflect inflammation and had a much lower 30% prevalence of neoplasia. These values are statistically significant with $p < 0.05$. Cases with abnormal light chain ratios demonstrated high levels of severity.

Monitoring of sFLC is advisable for evaluation of adverse events following COVID-19 vaccination based on the work of Malecka-Gieldowska, et al., Gudowska-Sawczuk, et al., and was affirmed in this study.[1,2] Serum free light chains have proven valuable for detection and monitoring neoplasia of the hematopoietic system and more recently in cases of inflammatory disease. These findings imply that COVID-19 and COVID-19 mRNA vaccines may have a role in inducing both neoplastic, paraneoplastic monoclonal proliferation and polyclonal inflammatory immune responses.

The possibility of malignant transformation justifies serial sFLC determinations in cases of abnormal values for κ and λ even with normal ratios. Additional research is required to explore this subject in greater depth.

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