LabMed

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Comparison of Two Different Integration Methods for Quantifying Monoclonal Proteins on Agarose Gel and Capillary Zone Electrophoresis Instruments

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Abstract: Quantifying M-proteins is an important part of diagnosing and monitoring patients with monoclonal gammopathies. Historically, laboratories use one of two methods to accomplish this. The splice method utilizes a perpendicular drop on each side of the M-protein on the electrophoretogram. In contrast, the skim method applies a tangent skimming line connecting the points above the polyclonal background. In this study, we compared the bias between these two methods across two different instruments (Helena SPIFE 3000 and Sebia Capillarys 3) in 118 patients. First, we compared the splice technique on both instruments and observed a significant average bias of 58.3% (slope = 1.437, y-intercept = 0.76, and r = 0.9682). We next compared the splice technique on the SPIFE 3000 to the skim technique on the Capillarys 3 and observed an average bias of only −2.10% (slope = 1.363, y-intercept = −1.98, and r = 0.9716), although there was significant scatter along the line of best fit. Lastly, we compared splice vs. skim on the Capillarys 3 and observed an average bias of −38.2% (slope = 0.947, y-intercept = −2.65, and r = 0.9686). Based on these results, care should be taken when switching instruments or integration techniques to ensure consistent monitoring of patients.

Keywords: multiple myeloma; monoclonal protein; M-protein; gel electrophoresis; capillary zone electrophoresis

Citation: Larkin, B.; Mahaney, L.; Abegunde, S.; Shea, J.L. Comparison of Two Different Integration Methods for Quantifying Monoclonal Proteins on Agarose Gel and Capillary Zone Electrophoresis Instruments. *LabMed* **2024**, *1*, 14–21. https://doi.org/10.3390/labmed1010004

Academic Editors: Sanghoon Song and Weiyong Liu

Received: 20 August 2024
Revised: 1 October 2024
Accepted: 16 October 2024
Published: 24 October 2024

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1. Introduction

Multiple myeloma (MM) is the second most common hematological cancer characterized by the infiltration and accumulation of malignant plasma cells in the bone marrow. The proliferating malignant plasma cells secrete abnormal immunoglobulins (monoclonal proteins, M-proteins) into the serum [1–4]. The quantification of M-proteins plays an important role in the diagnosis and monitoring of patients with MM and other plasma cell dyscrasias. The current guidelines by the International Myeloma Working Group (IMWG) and the National Comprehensive Cancer Network recommend an initial MM screening via serum protein electrophoresis (SPEP) and a serum free light chain assay followed by immunofixation electrophoresis (SIFE) if either are abnormal [5–7]. In this manner, SPEP is used to quantify the amount of M-protein present in a patient's serum; however, it cannot determine the isotype of the M-protein [2–6,8]. Therefore, follow-up testing with SIFE is performed in newly diagnosed patients for this purpose.

The accurate quantification of M-proteins is vital in the diagnosis, monitoring, and risk stratification of MM. M-proteins are quantified by measuring the area under the curve of an abnormal peak on an electrophoretogram generated by SPEP and multiplying by the total protein concentration in serum. Although the IMWG guidelines are applicable globally, no

guidance is provided within these guidelines on how best to measure the area under the curve. Hence, there are variations across different laboratories when measuring M-proteins via SPEP. Specifically, some labs employ a splice method for M-protein quantification that utilizes a perpendicular drop on each side of the M-protein on the electropherogram. Tangential skimming (the "skim method") is an alternative quantification method recently described by Willrich et al. [9] that involves applying a tangent skimming line connecting the points above the polyclonal immunoglobulin background.

Historically, the splice method has been used by most laboratories; however, emerging reports using proficiency testing samples suggest that the amount of polyclonal background in the samples affects this method more than the skim method, which may lead to the overestimation of M-proteins [9]. The overestimation increases in the splice method as the M-protein concentration decreases and the contribution of the polyclonal background subsequently increases [9]. This has also been demonstrated by others [10–12] and is especially prominent when the M-protein concentration is <15 g/L [12]. Despite these limitations regarding the splice method, it is still the most common quantification method used in clinical laboratories [4].

Historically, the method used for the semi-quantitative measurement of M-proteins in our lab was agarose gel electrophoresis on a Helena SPIFE 3000 instrument with M-protein integration performed using the splice technique. Following the purchase of a new instrument (Sebia Capillarys 3), we performed a bias assessment comparing M-protein quantification using the historical method/integration technique with both splice and skim integration techniques on the new instrument. The results of these experiments are presented below, including the impact at specific clinical cut points. The goal of this work was to minimize the bias when switching to the new instrument and ensure consistent monitoring of our patients.

2. Materials and Methods

2.1. Participants

A retrospective study was performed on 118 unique patients who had a physician's request for SPEP and measurable M-protein(s) migrating in the gamma region. Samples were collected between 24 February 2021 and 17 May 2022. From these patients, 167 samples were quantified using the splice method on the Helena SPIFE 3000, while 172 samples were quantified using both the splice and skim methods on the Sebia Capillarys 3 instrument. These analyses yielded 209 and 214 M-proteins, respectively. This study was approved by the Research Ethics Board of Horizon Health Network (Protocol Code 2022-3118, Approved 14 April 2022), and a waiver of consent for secondary use of personal information was obtained in accordance with the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2) requirements.

2.2. Data Collection and M-Protein Quantification

Aliquots from the same serum sample were run on both an SPIFE 3000 (Helena Laboratories, Beaumont, TX, USA), which uses agarose gel electrophoresis, and a Capillarys 3 (Sebia, Montreal, QC, Canada), which uses capillary zone electrophoresis. Gels generated from the SPIFE 3000 instrument were scanned, and M-proteins were quantified using densitometry and measurement of area under the curve using the vendor's software. For the Capillarys 3 instrument, M-proteins were also quantified in the same manner using the curve generated by the instrument's software (Phoresis, Version 9.30). In both cases, M-proteins were initially quantified by trained medical laboratory technologists according to standard operating procedures in our laboratory followed by Clinical Biochemist review prior to sign out. For the splice quantification method, M-proteins were integrated down to baseline (see Figure 1A for an example patient from this study). For the skim method, M-proteins were integrated by applying a tangent skimming line connecting the points above the polyclonal immunoglobulin background (Figure 1B). The software enabled the

technologist to easily toggle back and forth between splice and skim once the boundaries of the abnormal peak were identified by them.

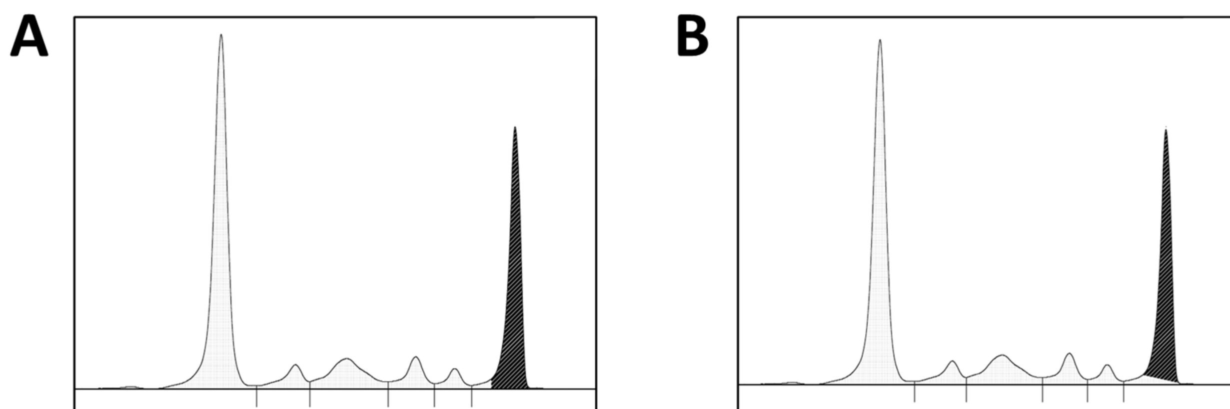

Figure 1. Example of quantifying a M-protein using the splice method (**A**), which uses a perpendicular drop on either side of the abnormal peak, and using the skim method (**B**), which uses tangential skimming connecting the base of the peak above the polyclonal background.

The data extraction process involved using Permanent Patient Record Numbers (PPRNs) and accession numbers. All data collected for use in this study were securely compiled into a dedicated database, adhering to strict privacy and confidentiality measures.

2.3. Bias Evaluation and Data Analyses

We assessed bias between the SPIFE 3000 splice and Capillarys 3 splice. We also determined the bias between SPIFE 3000 splice and Capillarys skim as well as Capillarys 3 splice and skim. Due to the retrospective nature of this study, we could not compare the SPIFE 3000 skim to the Capillarys 3 as we had not used this integration technique in our lab historically. Agreement was assessed using Deming linear regression analysis and absolute and percentage bias plots. Additionally, the bias at the clinical decision point of 30 g/L [2,3] was calculated from the equation determined by the Deming regression analyses. A difference of ±25%, derived from The Institute for Quality Management in Healthcare Allowable Performance limits, was considered clinically significant. All statistical analyses of results were performed using EP Evaluator, Version 12.3.0.2 (Data Innovations, Colchester, VT, USA).

3. Results

3.1. SPIFE 3000 Splice vs. Capillarys 3 Splice

Of the 214 distinct M-proteins analyzed in this study, 206 were compared using the SPIFE 3000 splice method vs. the Capillarys 3 splice method. Eight samples were excluded because of missing data in the SPIFE dataset. The M-protein concentrations ranged from 0.4 to 34.6 g/L when measured using the SPIFE 3000 software and from 0.3 to 49.8 g/L when measured on the Capillarys 3. Figure 2 shows the Deming regression (A) and bias (B, C) plots for this comparison. The slope was 1.437 (95% CI, 1.387–1.487), the y-intercept was 0.76 (95% CI, 0.37–1.14), and the correlation coefficient was 0.9682. The average bias across all the samples was 58.3%, indicating that the M-protein concentration can differ by instrument as it is significantly higher when determined on the Capillarys 3 using the sample integration technique compared to the SPIFE 3000. At the clinical cut point of 30 g/L with the SPIFE 3000, the estimated Capillarys 3 value using the regression equation (e.g., Capillarys 3 value = 1.437 (30 g/L) + 0.76) was also significantly higher at 43.9 g/L (95% CI, 42.6–45.1), representing a difference of 46.3% (Table 1).

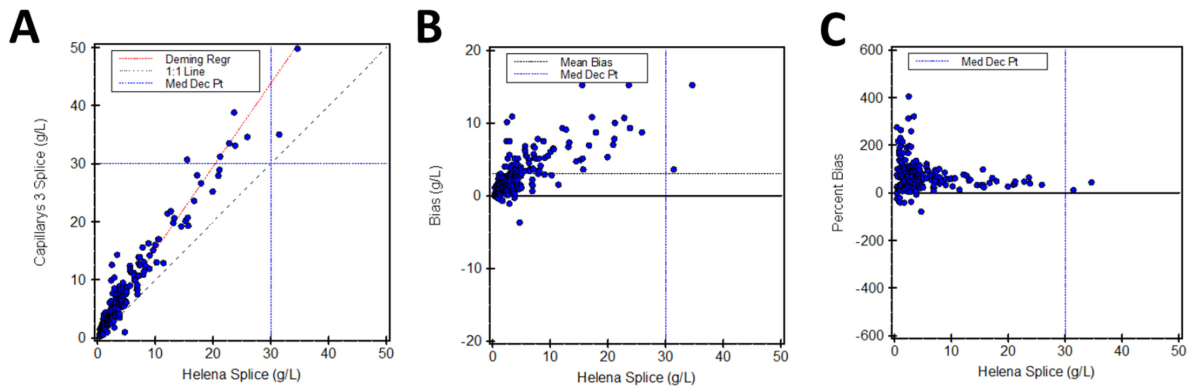

Figure 2. Deming Regression (**A**) and absolute bias (**B**) and % bias plots (**C**) of M-proteins quantified on a Helena SPIFE 3000 instrument versus a Sebia Capillarys 3 instrument using a splice integration technique (n = 206). The predicted equation from Deming Regression is y = 1.437x + 0.76. A medical decision point of 30 g/L is depicted on the graph by the dotted blue line.

Table 1. Predicted values using the regression equation at the clinical cutpoint of 30 g/L. For each regression equation, a value of 30 g/L was input as the x-value to give a predicted y-value.

X Method	Y Method	Regression Equation	Predicted "Y" Concentration at Clinical Cut Point of 30 g/L (95% CI)	% Difference from 30 g/L
SPIFE 3000 Splice	Capillarys 3 Splice	y = 1.437x + 0.76	43.9 g/L (42.6–45.1)	46.3%
SPIFE 3000 Splice	Capillarys 3 Skim	y = 1.363x − 1.98	38.9 g/L (37.8–40.1)	29.7%
Capillarys 3 Splice	Capillarys 3 Skim	y = 0.947x − 2.65	25.8 g/L (25.0–26.5)	−14.0%

3.2. SPIFE 3000 Splice vs. Capillarys Skim

Given the significant positive bias we observed when comparing the Capillarys 3 splice method to the SPIFE 3000 splice method, we sought to compare the SPIFE splice to the Capillarys skim. Ultimately, our goal was to ensure that there were no significant shifts in the patient results when switching to the new Capillarys 3 instrument.

For these analyses, 207 M-proteins were measured. The M-protein concentration as determined by the SPIFE 3000 was the same as above (0.4–34.6 g/L) compared to <0.1–48.3 g/L as determined on the Capillarys 3 using the skim integration method. Figure 3 shows the Deming regression (A) and bias (B, C) plots for this comparison.

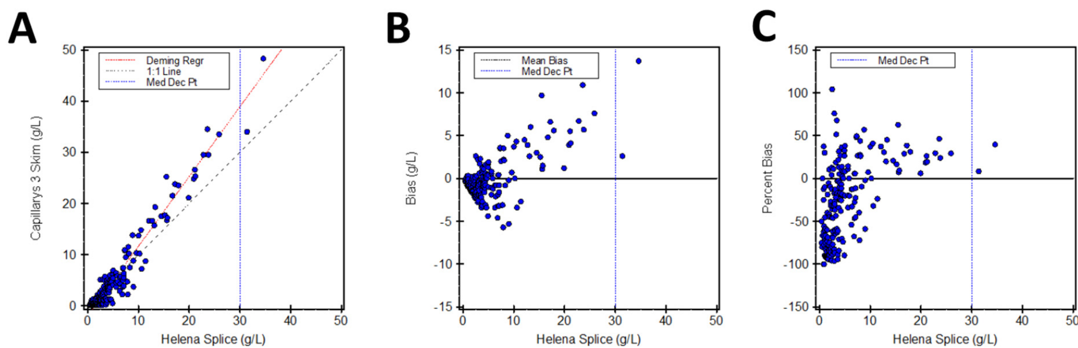

Figure 3. Deming Regression (**A**) and absolute bias (**B**) and % bias plots (**C**) of M-proteins quantified on a Helena SPIFE 3000 instrument using a splice integration technique versus a Sebia Capillarys 3 instrument using a skim integration technique (n = 207). The predicted equation from Deming Regression is y = 1.363x − 1.98. A medical decision point of 30 g/L is depicted on the graph by the dotted blue line.

The slope was 1.363 (95% CI, 1.319–1.408), the y-intercept was −1.98 (95% CI, −2.33 to −1.64), and the correlation coefficient was 0.9716. The average bias across all the samples

was much lower compared to the first comparison at −2.10%, although there was significant scatter along the line of best fit (Figure 3). This difference represents the sum of the bias between the two instruments and the two integration techniques. At the clinical cut point of 30 g/L using the SPIFE 3000, the estimated Capillarys 3 skim value using the regression equation was 38.9 g/L (95% CI, 37.8–40.1), which represents a difference of 29.7% (Table 1).

3.3. Capillarys Splice vs. Capillarys Skim

Given the bias observed in the above experiments, we wanted to determine if the reason for this was solely due to the differences in the integration technique. Therefore, a comparison was performed between the Capillarys 3 splice and the Capillarys 3 skim to determine if the agreement was better.

For these analyses, 211 M-proteins were measured. The M-protein concentration for the splice method ranged from 0.3 to 49.8 g/L, and, for the skim method, it ranged from <0.1 to 48.3 g/L. Figure 4 shows the Deming regression (A) and bias (B, C) plots for this comparison.

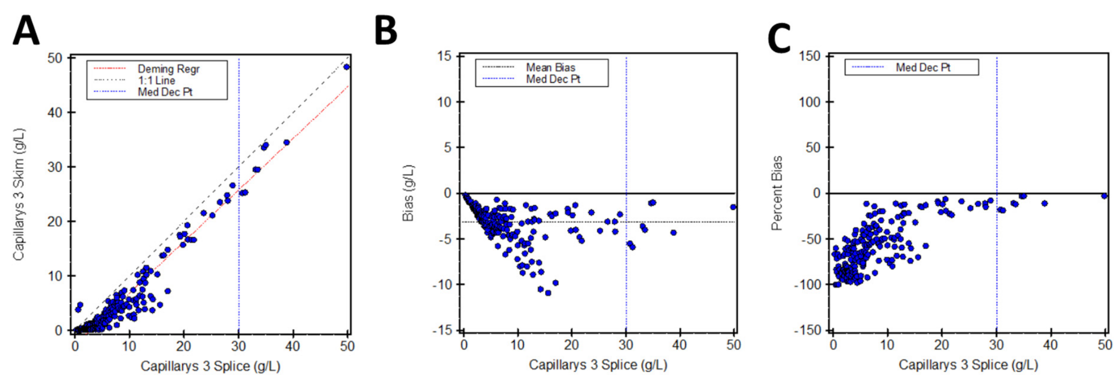

Figure 4. Deming Regression (**A**) and absolute bias (**B**) and % bias plot (**C**) of M-proteins quantified on a Sebia Capillarys 3 instrument using a splice vs skim integration technique (n = 211). The predicted equation using Deming Regression is y = 0.947x − 2.65. A medical decision point of 30 g/L is depicted on the graph by the dotted blue line.

The slope was 0.947 (95% CI, 0.915–0.979), the y-intercept was −2.65 (95% CI, −3.02 to −2.28), and the correlation coefficient was 0.9686. The average bias across all the samples was −38.2%, although the largest differences were observed in the lower concentration range (<15 g/L), specifically when there was an increase in the polyclonal immunoglobulins (Figure 5). In this scenario, there appeared to be an overestimation of the M-protein concentration using the splice technique versus the skim technique. At the clinical cut point of 30 g/L using the splice method, the estimated Capillarys 3 skim value using the regression equation was lower at 25.8 g/L (95% CI, 25.0–26.5), which represents a difference of −14.0% (Table 1).

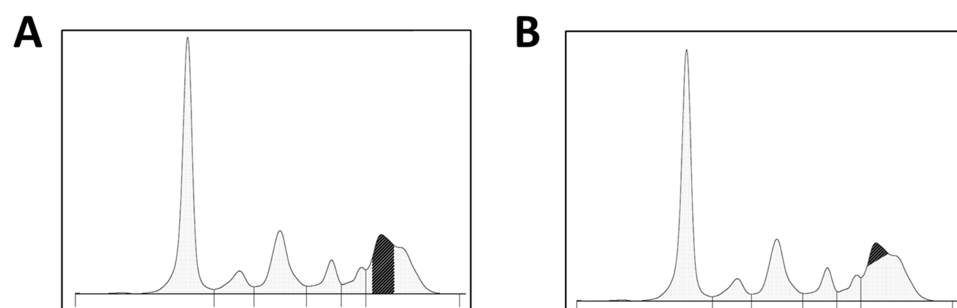

Figure 5. Quantification of an M-protein using the splice (**A**; M-protein = 10.9 g/L) versus skim technique (**B**; M-protein = 2.2 g/L) of the same sample on a Capillarys 3 instrument with a polyclonal increase in gamma globulins.

4. Discussion

The quantification of M-proteins is essential in the diagnosis and monitoring of MM. M-proteins are typically measured using serum protein electrophoresis (SPEP), followed by quantification using either the splice or skim technique. The splice method includes the polyclonal background within the M-protein peak, which may lead to the overestimation of the M-protein concentration [13]. In contrast, the skim method aims to mitigate this issue by excluding the polyclonal background. In the current study, we compared both techniques across two different instruments, the Helena SPIFE 3000 and Sebia Capillarys 3. We observed a significant bias between the two integration methods as well as between the two instruments, particularly in patients with a polyclonal increase in gamma globulins as well as at the clinical cut point of 30 g/L.

Our analysis revealed a significant bias when comparing the SPIFE 3000 splice method with the Capillarys 3 splice method. The average bias of 58.3% between the two instruments was outside our total allowable error goal of ±25%. At the clinical decision point of 30 g/L, the Capillarys 3 instrument generated M-protein results that were significantly higher compared to the SPIFE 3000. Since the same integration technique was used in this experiment, it suggests that differences in electrophoresis technologies (gel vs. capillary) contribute to measurement discrepancies. This finding is consistent with prior studies that have shown differences between gel and capillary electrophoresis for the detection and quantification of M-proteins [14]. Specifically, McCudden et al. observed a positive bias using capillary compared to gel electrophoresis for the quantification of M-proteins in 42 specimens, specifically when the M-protein concentration was <10 g/L. This agrees with our study, which utilized a larger sample size. In contrast, Katzman et al. observed good agreement between capillary and gel electrophoresis when the M-protein concentration was <20 g/L; in their study, a positive bias was only observed in those samples where the M-protein concentration was >20 g/L [15]. The reason for this difference is unclear but may be due to the fact that different instruments (and instrument manufacturers) were used.

To ensure consistency among our patients when switching between the SPIFE 3000 and the Capillarys 3, we next compared the SPIFE 3000 splice method to the Capillarys 3 skim method to see if this reduced the bias. It is important to note that the bias observed in this comparison represents the sum of the bias between the instruments and integration technique. With this comparison, we observed an average bias of −2.10%, which is within our total allowable error goal. However, there was significant scatter around the line of best fit, which indicates that there may be patient/sample-specific differences between the two methods. In addition, the bias remained significant at the clinical cut point of 30 g/L (29.7%), although it was lower compared to the splice vs. splice comparison. For this reason, we chose to implement the skim integration technique in our laboratory when switching from the SPIFE 3000 to the Capillarys 3 after consulting with clinical stakeholders. Specifically, the oncology team wanted to ensure that any change in the M-protein concentration was mostly reflective of a change in the disease state and not reflective of just a change in instrument.

Others have reported that the skim method provides better alignment by reducing the influence of polyclonal immunoglobulins [11,12]. Miller et al. compared the quantification of M-proteins using two peak-integration protocols across multiple electrophoresis platforms, similar to our study, and found that the skim method consistently provided more reliable measurements, emphasizing its effectiveness in minimizing the impact of polyclonal immunoglobulins [11]. Similarly, Schild et al. demonstrated that the skim method provided superior reliability in M-protein quantification [12]. These previous studies, in combination with the results of our study, provided further evidence to support the change to the skim integration technique when moving to the Capillarys 3.

Lastly, we compared the splice versus skim M-protein integration techniques on the same instrument (Capillarys 3), which revealed an average bias of −33.2%. Significant discrepancies were particularly evident in samples with M-protein concentrations below 15 g/L, where polyclonal immunoglobulins disproportionately affected the splice method.

These results corroborate the findings of others [10–12]. Schild et al., who first described the skim method, demonstrated that the splice method is prone to overestimation in the presence of a polyclonal background, particularly at concentrations below 10–20 g/L [12]. Additionally, a study conducted by Keren et al. demonstrated that, while the splice method can sufficiently quantify high M-protein concentrations where there is suppression of the polyclonal background, there could be an overestimation of as much as 50% at lower concentrations below 10–20 g/L [10]. These previous studies, along with our findings, highlight that the skim method reduces the variability caused by polyclonal immunoglobulins, resulting in more consistent results.

Some laboratories advocate that the choice of which integration technique to use should be sample-dependent, and that the decision should be made prior to the M-protein quantification. The parameters that may be considered when making this decision include the relative amount of monoclonal versus polyclonal proteins and the migration location (e.g., M-proteins migrating in the beta region), etc. However, this would require having very well-defined criteria for when to use each technique. To the best of our knowledge, no such guidelines are currently available in the literature; therefore, the use of the same integration technique across all the samples is the most appropriate to ensure consistent monitoring.

Although we have shown that significant differences exist between methodology (gel vs. capillary) and M-protein integration technique (splice vs. skim), our study is not without limitations. Specifically, the comparison that yielded the lowest percentage difference between the patients (SPIFE 3000 splice vs. Capillarys 3 skim) represents the sum of the bias between the instruments and integration techniques. Our study would have been improved had we had skim measurements available for comparison on both instruments. Furthermore, while the sample size is adequate for statistical analysis, it may not fully represent the variability observed in a larger, more diverse population. The subjective nature of the quantification process for both the splice and skim methods and the involvement of different technologists in performing the measurements may also introduce error. However, we perform annual comparisons between each of the technologists that work in this area of our laboratory to ensure consistent M-protein quantification (<5% inter-operator variability). Future studies should aim to include larger cohorts and consider prospective designs to further validate these findings.

5. Conclusions

Our study highlights significant biases between the splice and skim methods for M-protein quantification across two different electrophoresis platforms. Utilizing the skim method on a Capillarys 3 instrument reduced the overestimation observed with the traditional splice method on the Helena SPIFE 3000 instrument, particularly at lower M-protein concentrations. Given these findings, clinical laboratories should consider transitioning to the skim method to provide better estimates of the M-protein concentration. Most importantly, laboratories need to ensure that they are providing consistent results over time for their patients, especially when switching instruments. Future research should focus on validating these results in larger prospective studies and exploring the clinical implications on patient management and patient outcomes.

Author Contributions: Conceptualization, J.L.S.; methodology, S.A. and J.L.S.; validation, B.L and L.M.; data curation and analysis, B.L. and L.M.; writing—original draft preparation, B.L. and J.L.S.; writing—review and editing, L.M. and S.A.; supervision, J.L.S. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Horizon Health Network (Protocol Code 2022-3118, Approved 14 April 2022).

Informed Consent Statement: A waiver of consent for secondary use of personal information was approved by the Institutional Review Board of Horizon Health Network in accordance with the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2) requirements.

Data Availability Statement: The data presented in this study are available upon request from the corresponding author due to ethical reasons.

Acknowledgments: We would like to thank the following staff who helped with data extraction and running specimens on the instruments: Susan Scott, Cory Miller, Kayla Sturgeon, and Kate-Lyn Tibbet.

Conflicts of Interest: The authors declare no conflicts of interest.

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