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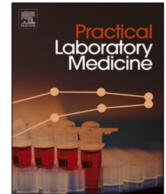

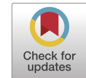

A Comparison of gel (Hydragel 30) and capillary (Capillarys III Tera) electrophoresis for the characterization of human serum proteins

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ABSTRACT

Objectives: To compare gel (Hydrasys 2 from Sebia) and capillary (Capillarys III Tera, Sebia) electrophoresis for the characterization of human serum proteins.
Design and methods: 304 sera tested by gel electrophoresis during 8 routine laboratory days were concurrently tested by capillary electrophoresis. Gels were read by an experienced medical technologist while capillary profiles by a Sebia representative and the same technologist. Most sera (214 of 304, 70%) were also analyzed by immunofixation electrophoresis, used here as the gold standard to calculate sensitivity and specificity of the gel and capillary systems.
Results: Gel and capillary estimated the concentration of albumin, gamma region, and M-spikes nearly perfectly, and that of beta, alpha-2, and alpha-1 regions with excellent correlation. The two systems classified concordantly 268 of 304 sera (88% agreement) as having no, one, or two M-spikes, but differed in the remaining 36 sera (12%). Gel electrophoresis correctly identified M-spikes in 82 of 112 sera that were shown to have monoclonal band(s) by immunofixation (73% sensitivity), and correctly did not reveal M-spikes in 97 of the 102 sera that had no immunofixation bands (95% specificity). Capillary achieved slightly higher sensitivity (85 of 112, 76%) and slightly lower specificity (94 of 102, 92%), but the two areas under the ROC curves were nearly identical at 0.84.
Conclusions: Gel and capillary electrophoresis systems perform similarly to estimate the concentration of serum protein fractions and detect M-spikes.

1. Introduction

The electrophoresis of serum proteins remains a laboratory cornerstone for the diagnosis and monitoring of patients with plasma cell disorders (such as monoclonal gammopathy of undetermined significance, multiple myeloma, Waldenström macroglobulinemia, and AL amyloidosis). These conditions have a relatively high prevalence in the general population, so that effective detection modalities are critical. The monoclonal gammopathy of undetermined significance, for example, affects approximately 3% of individuals over the age of 50 when analyzed by serum protein electrophoresis and free light chains [1,2], and 5% when analyzed by mass spectrometry [3]. Once a monoclonal immunoglobulin (commonly called M-spike or M-protein) is identified by electrophoresis and a

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diagnosis of plasma cell dyscrasia established, its concentration can be used to monitor disease progression and response to treatment, as well as for prognosis.

Following the pioneering studies of Arne Tiselius [4], which led to his Nobel prize award in 1948, electrophoresis has markedly improved through the decades thanks to the introduction of solid support media. These media have evolved from paper to cellulose acetate [5], to agarose gel [6], and to thin-layer agarose gel, allowing the distinction of serum proteins into five fractions: albumin, alpha-1, alpha-2, beta, and gamma. A newer version, called high-resolution thin-layer agarose gel, splits the beta region into two components: beta-1 (transferrin) and beta-2 (complement 3). In normal subjects, these five (or six) serum protein fractions are symmetric, that is they resemble the shape of a bell curve, although some asymmetry can be seen in the gamma region even in health, reflecting the different compositions of the antibody repertoires. Following the separation on thin-layer agarose gel, serum proteins are stained with amido black and scanned to generate an electrophoretogram that corresponds to the protein concentration. Delimiters are then placed to demarcate each fraction and M-spikes.

More recently, analysis of liquid media by capillary electrophoresis was developed [7] and applied to the analysis of serum proteins for clinical purposes [8,9]. Here proteins are separated by applying high voltage to an array of open glass capillary tubes (one per sample), and their concentration estimated directly by measuring the absorption of the peptide bond at around 200 nm. Like the high-resolution thin-layer agarose gel electrophoresis, capillary electrophoresis offers a greater resolution of the beta region by resolving it into two fractions and thus increasing the likelihood of detecting low-concentration monoclonal immunoglobulins that migrate to this region, since in standard thin-layer agarose gel electrophoresis they can be obscured by transferrin, complement C3, or beta-lipoprotein [10]. Besides being more amenable to automation, capillary also has the technical advantage of measuring proteins directly (by their peptide bond absorption, rather than by their binding affinity to a dye). This feature increases the resolution of the electrophoretogram curves, thus increasing the ability to recognize irregularities. At the same time, it has the drawback that every substance absorbing around 214 nm is detected, not just the proteins, such as some antibiotics [11] and radiocontrast media [12].

Gel electrophoresis remains the method used by most clinical laboratories in the United States. For example, in the September 2020 survey of the College of American Pathologists, of the total 676 clinical laboratories that performed the serum protein electrophoresis test and participated to this national survey, 364 (54%) did so by gel electrophoresis and 312 (46%) by capillary electrophoresis (see Supplemental Fig. 1A). Nevertheless, usage of gel electrophoresis is gradually decreasing while that of capillary electrophoresis increasing.

Previous studies have compared gel to capillary electrophoresis [8,13–15] and shown excellent agreement (>95%) in determining the concentration of the five serum protein fractions (albumin, alpha-1, alpha-2, beta, and gamma). Goal of the present study was to compare the performance of gel electrophoresis to that of the new capillary electrophoresis apparatus Capillarys III Tera (Sebia, Lisses, France) in a routine clinical setting at a tertiary referral hospital, using a large patient population and focusing on the characterization of the M-spike. M-spikes of sufficient amount (≥0.5 g/dL), when analyzed by either gel or capillary electrophoresis, appear as an additional fraction (band, peak) in the gamma region, more rarely as an increase of the normal beta region(s), and extremely rarely as an increase of the normal alpha-2 region. M-spikes of lower amount (between 0.1 and 0.4 g/dL), instead, do not manifest as distinct bands but rather as asymmetries (deformities, irregularities) in the shape of the electrophoretogram curves. M-spikes of even lower amounts (<0.1 g/dL) cannot be detected by electrophoresis and requires instead immunofixation electrophoresis (which is about 10-fold more sensitive than regular electrophoresis, at around 0.01 g/dL) or mass spectrometry [3,16].

2. Materials & methods

2.1. Study population and laboratory setting

The study included all serum samples analyzed by the immunology laboratory for routine clinical purposes over the course of 8 days during the months of October and November 2019, totaling 304 sera (no samples were excluded from the analysis, with the exception of a 2-month old neonate since all of the remaining participants were adults). There were 160 females (62 ± 16 years, range 19–95) and 144 males (65 ± 14 years, range 23–97), with no significant difference in age according to sex. The immunology laboratory serves a large inpatient and outpatient population, and performs protein electrophoresis mainly for oncology, neurology, and rheumatology patients. Sera were de-identified and disposed after use; therefore, the study qualified as exemption 4.

2.2. Electrophoresis of serum proteins by gel

Sera were first ran using the system currently in use, which consists of a thin-layer agarose gel (HYDRAGEL 30 Protein (E), from Sebia, Lisses, France) and the Hydrasys 2 semi-automated analyzer. Electrophoresis was performed according to the manufacturer's recommendations. Briefly, sera (10 μL) were applied to the wells of the applicator and incubated for 5 min in a humid chamber; the applicator was then positioned onto a pre-wet agarose gel and electrophoresis performed in alkaline buffer at constant 20 Watts for a total of 33 V/h. After drying, the gel was stained using amido black, de-stained, and scanned using the Sebia GELSCAN densitometer to convert the band intensity into electrophoretogram fractions. The area under the curve of each fraction was used to calculate its concentration in g/dL from the total area under the curve, which corresponded to the serum total protein concentration. This concentration was obtained using Roche Total Protein Gen.2 reagent on the Optilite turbidimeter (The Binding Site, Birmingham, UK). The stained gel and electrophoretograms were visually interpreted by a technologist and one of us to confirm the appropriate positioning of the delimiters and marking of M-spike(s) when present. M-spikes were delimited using the perpendicular drop, thus including the polyclonal background, if present, in the quantification. When two or more M-spikes were seen, they were labeled sequentially from

the anodal to the cathodal side of the electrophoretogram.

2.3. Electrophoresis of serum proteins by capillary

Sera were then assayed on the Capillarys III TERA automated analyzer using CAPI 3 Protein (E) reagents, both provided by Sebia (Lisses, France). Electrophoresis was run according to the manufacturer's recommendations. Briefly, serum proteins were diluted in analysis buffer and separated by electrophoresis in alkaline buffer under constant voltage for about 4 min. Proteins were directly

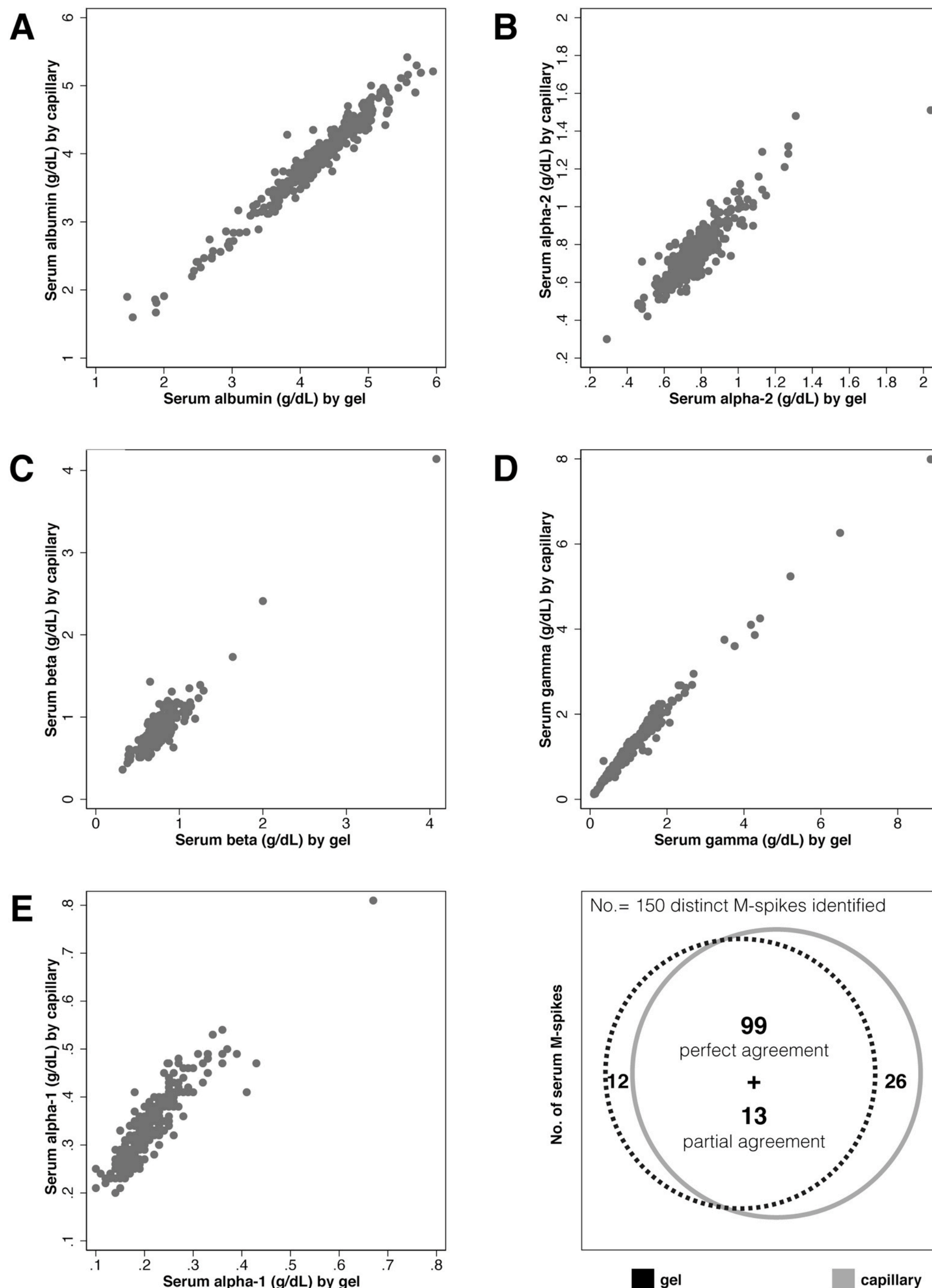
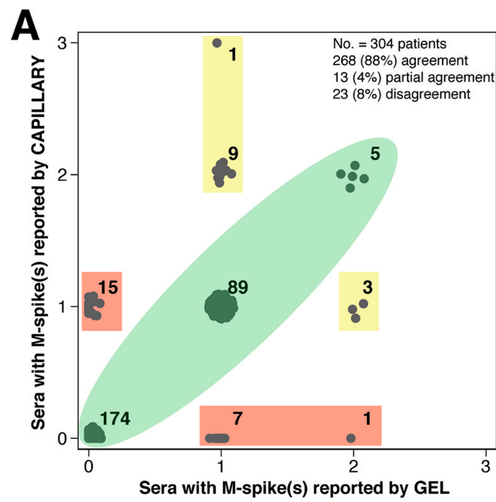
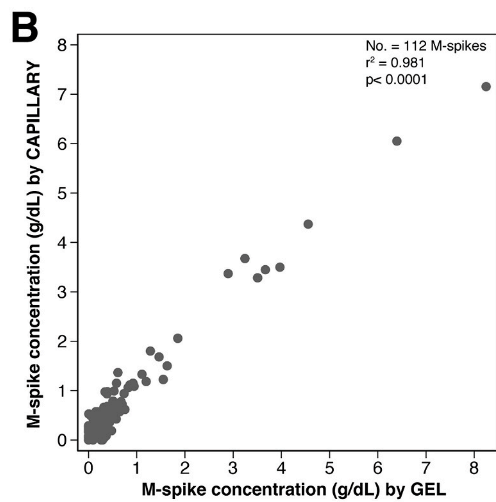


Fig. 1. A-E. Correlation between gel and capillary electrophoresis in estimating the concentration of the five serum protein fractions in 304 sera: albumin (A), alpha-2 (B), beta (C), gamma (D), and alpha-1 (E). **F.** Overall number of M-spikes identified by gel and/or capillary electrophoresis in the 304 sera.





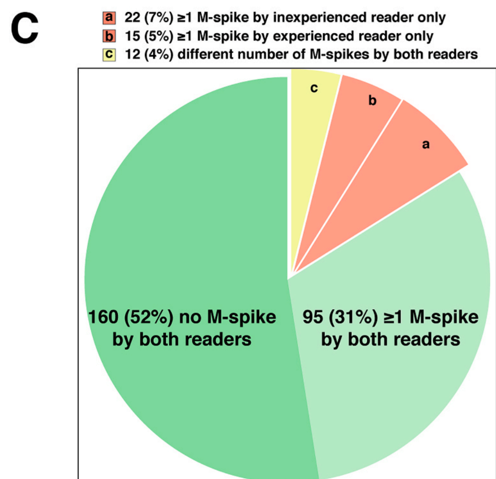


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Fig. 2. **A**. Classification of serum M-spikes by gel and capillary electrophoresis. The green shaded area indicates perfect agreement, the yellow area partial agreement, and the red area disagreement. **B**. Correlation between gel and capillary electrophoresis in estimating the concentration of M-spikes. **C**. Comparison of the readings of 304 sera analyzed by capillary electrophoresis between experienced and inexperienced reader. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

estimated by measuring the absorbance of their peptide bonds at 200 nm, and used to draw an electrophoretic pattern by the Phoresis software. Protein concentration (in g/dL) was then calculated as above from the serum total protein concentration. All electrophoretograms were interpreted by an experienced Capillarys reviewer from the Sebia's Result Interpretation Escalation Team and, independently, inexperienced reader. As done for the gel electrophoresis readings, when two or more M-spikes were seen, they were labeled from left to right.

2.4. Serum immunofixation electrophoresis

Serum immunofixation electrophoresis (SIFE) was performed in 214 of the total 304 sera because already ordered by the provider for most cases. Sera were pre-diluted according to the immunoglobulin G, A, and M concentrations, and then ran on the immunofixation system currently in use, which consists of a thin-layer agarose gel (HYDRAGEL IF 2/4, from Sebia, Lisses, France) and the Hydrasys 2 semi-automated analyzer. Electrophoresis was performed in an alkaline buffer at constant 20 Watts for a total of 42 V/h. Following the migration, serum proteins were incubated for 6 min with Sebia secondary antibodies directed against IgG, IgA, IgM, kappa, or lambda. After drying, the gel was stained using acid violet and appropriately de-stained. All IFE gels were interpreted by two experienced readers.

2.5. Statistical analyses

Differences among the proportions of positive/negative results between the two analyzers were assessed by chi-squared. Correlations between the concentration of the various serum protein fractions and M-spikes were evaluated by simple linear regression. Sensitivity and specificity of gel and capillary electrophoresis were assessed using ROC curve analyses. Statistics was done using Stata statistical software, release 15.1 (Stata Corporation, College Station, TX).

3. Results & discussion

3.1. Gel and capillary electrophoresis correlate well for estimating the concentration of the five serum protein fractions

When the serum total protein concentration was entered into Phoresis software and then used to calculate the individual protein fractions, we obtained a highly significant ($p < 0.0001$) correlation between the gel and capillary electrophoresis values. In particular,

Table 1
Characterization of 304 sera by gel electrophoresis (GE) and capillary electrophoresis (CE), according to the number (0, 1, 2 or 3) of M-spike(s). The immunofixation electrophoresis (IFE) results in a subset of 214 of the 304 sera is also reported.

STANDARD ELECTROPHORESIS				IMMUNOFIXATION ELECTROPHORESIS				
No. of sera studied by GE and CE	Number of M-spike(s) by GE and/or CE	Total M-spikes by GE	Total M-spikes by CE	No. of sera also studied by IFE	0 band by IFE	1 band by IFE	2 bands by IFE	≥3 bands by IFE
174	0 M-spike detected by both GE and CE	0	0	114	92	12	8	2
89	1 M-spike detected by both GE and CE	89	89	64	3	49	11	1
5	2 M-spikes detected by both GE and CE	10	10	4	0	0	4	0
3	2 M-spikes detected by GE and 1 by CE	3 + 3*	3*	3	0	0	2	1
9	2 M-spikes detected by CE and 1 by GE	9*	9 + 9*	8	0	4	3	1
1	3 M-spikes detected by CE and 1 by GE	1*	2 + 1*	1	0	0	0	1
7	1 M-spike detected by GE but not by CE	7	0	6	2	3	1	0
1	2 M-spikes detected by GE but not by CE	2	0	1	0	0	1	0
15	1 M-spike detected by CE but not by GE	0	15	13	5	3	5	0
304		*124*	*138*	*214*	*102*	*71*	*35*	*6*

Note: The asterisk (*) indicates a partial agreement because, although M-spikes were reported by both GE and CE analyzers, one analyzer reported more total M-spikes than the other. The shadings represent the agreement between GE and CE: white, complete agreement; light gray, partial agreement; dark gray, complete disagreement.

serum albumin yielded an adjusted r-squared of 0.957 and a regression coefficient of 0.885 (Fig. 1A). Similarly, excellent r-squared values were obtained for the alpha-2 (0.810, Fig. 1B), beta (0.872, Fig. 1C), and gamma (0.979. Fig. 1D) fractions. On the contrary, for the alpha-1 fraction, the Capillarys analyzer yielded consistently higher values: for every unit increase (g/dL) in the gel values, the capillary values increased by 1.14, meaning they were on average 14% higher, with a 95% confidence interval going from 7% to 20% (Fig. 1E). This discrepancy, originally reported by Bossuyt and colleagues [17], is caused by the inability of alpha-1 acid-glycoprotein, an important component of the alpha-1 region, to effectively bind the amido black used to stain electrophoresis gels. Since Capillarys detects absorption of peptide bonds, rather than affinity of the protein to amido black, it estimates the protein concentration of the alpha-1 region more accurately.

3.2. Characterization of the serum M-spike number

Of the total 304 sera, 174 were reported as having no M-spike, 89 one M-spike, and 5 two M-spikes by both analyzers, for an overall percent agreement of 88% (268 of 304, green shaded area in Fig. 2A). The remaining 36 sera, on the contrary, differed either because one instrument reported an M-spike whereas the other one didn't (No. = 23, red shaded area), or because one instrument reported more M-spikes than the other (No. = 13, yellow shaded area).

These discrepant 36 sera contributed a total of 64 M-spikes: 12 M-spikes were reported only by gel, 26 only by capillary, and 13 by both instruments (Fig. 1F, Table 1). Of these 64 M-spikes, there was complete disagreement in 24 and partial disagreement in the remaining 40 (Table 1). Comparing the two analyzers in terms of M-spike by linear regression yielded an adjusted r-squared value was 0.729, with a p-value < 0.0001 (Fig. 2A).

3.3. Characterization of the serum M-spike concentration

A total of 112 M-spikes were reported by both gel and capillary electrophoresis, either with perfect agreement, No. = 99, or partial disagreement, No. = 13, thus allowing us to compare their concentration. This total comes from 89 sera were one spike was reported by both analyzers, 5 sera where two spikes were reported by both analyzers (No. = 10 spikes), and 13 sera that, although discrepant overall, they did contain one spike where there was agreement. When analyzed by linear regression, the two analyzers correlated excellently in estimating the M-spike concentration: the adjusted r-squared was 0.981 with a p-value <0.0001 (Fig. 2B). The regression coefficient indicated that for every g/dL increase in the gel estimation, the capillary estimation changed by 0.91 g/dL, thus revealing on average a 10% lower M-spike concentration when using the capillary analyzer.

3.4. Characterization of the serum M-spike location

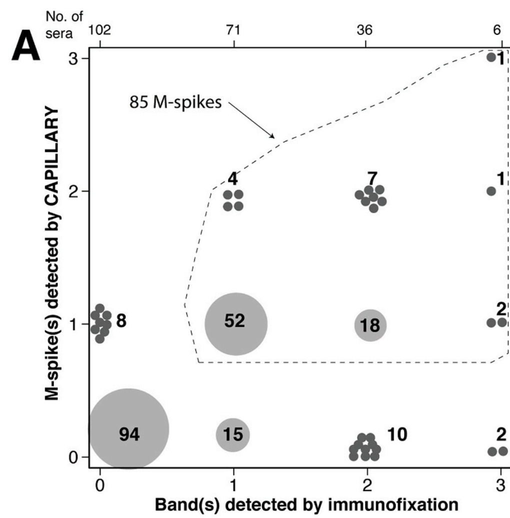
Of the total 150 reported M-spikes, 110 were reported by both analyzers, 107 placed in the gamma and 3 in the beta region (Table 2). The remaining 40 were assigned by either gel only (No. = 12) or capillary only (No. = 26), or by gel in the gamma region and capillary in the beta region.

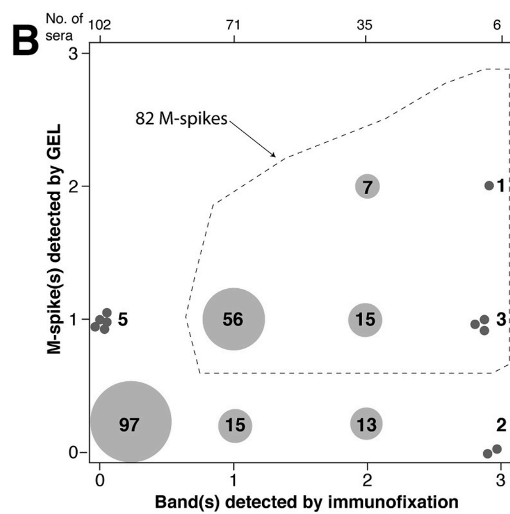
3.5. Comparison of experienced versus inexperienced readers in classifying serum M-spikes by capillary electrophoresis

To assess the efficacy and rapidity of implementing Sebia capillary electrophoresis in a clinical laboratory using Sebia gel electrophoresis, the entire dataset of 304 sera was read independently by an experienced Sebia reader, and the first author, a reader experienced with gel electrophoresis but new to capillary electrophoresis. The two readers agreed in 261 cases (83%), both classifying 166 cases (52%) as not having an M-spike and 95 (31%) as having one or more M-spikes (Fig. 2C, green-hued slices). The inexperienced reader identified more M-spikes than the experienced reader. In particular, 22 sera (7%) were classified as having one or more M-spike by the former that were instead considered negative by the later (Fig. 2C, slice a). On the contrary, only 15 sera (5%) were classified as having one or more M-spike by the experienced reader and instead considered negative by the inexperienced reader (Fig. 2C, slice b). In the remaining 12 cases (4%), M-spikes were reported by both reader but they differed in their number (Fig. 2C, slice c). Overall, the capillary system requires comprehensive training, even if the laboratory is already experienced in interpreting gel electrophoresis and using Phoresis software.

Table 2
Classification of the serum M-spike reported by gel and capillary electrophoresis according to their location.

		Capillary			
Gel		*Beta region*	*Gamma region*	*No spike reported*	
	Beta region	3	–	–	
	Gamma region	2	107	12	
	No spike reported	2	24	–	
					150





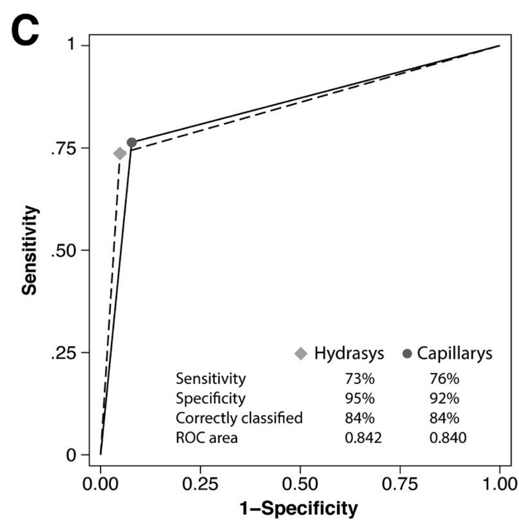


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Fig. 3. Comparison of standard electrophoresis, by capillary or gel, with immunofixation electrophoresis using 214 of the total 304 sera featured in the study. **A**. Comparison between serum M-spikes identified by capillary electrophoresis read by an experienced reader and immunofixation electrophoresis –**B**. Comparison between serum M-spikes identified by gel electrophoresis read by an experienced reader and immunofixation electrophoresis. **C**. ROC curve analysis for gel and capillary electrophoresis, showing the nearly identical performance of the two systems.

3.6. Comparison of accuracy between capillary and gel electrophoresis, using immunofixation as the gold standard

To compare the gel and capillary analyzers in terms of their ability to accurately identify M-spike as true monoclonal immunoglobulin bands, we performed immunofixation electrophoresis in 214 (70%) of the total 304 sera. Of these 214 sera, 102 were found to have no band of restricted mobility by immunofixation and 112 had one or more bands of restricted mobility; in particular, 71 sera had one band, 35 sera two bands, and 6 sera three or more bands (Table 1). Capillary correctly identified M-spikes in 85 of the 112 immunofixation bands, for a sensitivity of 76%, and correctly did not identify M-spikes in 94 of the 102 negative immunofixations, for a specificity of 92% (Fig. 3A). Similarly, the gel correctly identified as M-spikes 82 of the 112 immunofixation bands (73% sensitivity), and correctly did not identify M-spikes in 97 of the 102 negative immunofixations (95% specificity, Fig. 3B). ROC curve analysis showed the two analyzers had a nearly identical performance, with areas of 0.840 (95% CI from 0.793 to 0.888) for capillary and 0.844 (985% CI from 0.795 to 0.888) for gel electrophoresis (Fig. 3C).

In conclusion, gel and capillary electrophoresis perform very similarly to estimate the concentration of serum protein fractions and to identify and quantify M-spikes, in agreement with previous reports [8,13–15]. The Capillarys system has the disadvantages of a higher equipment cost and requiring a greater sample volume. On the other hand, Capillarys requires less involvement of laboratory technicians, offers a faster turn-around time, identifies the specimens at that are being analyzed, does not depend upon the chemicals needed to stain and destain the gels, and is more amenable to remote reporting.

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Declaration of competing interest

The authors declare no conflict of interest of any sort.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.plabm.2021.e00233.

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