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ORIGINAL ARTICLE

Validation Study on Auto Verification Rules for Routine Coagulation Tests

Linzi Miao, Anna Jiang, Yao Lu, Ran You, Chenxue Qu

Peking University First Hospital, Department of Clinical Laboratory, Beijing, China

ABSTRACT

Background: **Auto verification rules (automated rule-based validation and release of clinical test results without manual review) play a critical role in the reporting of coagulation test results in clinical laboratories. While such rules have been established for routine coagulation assays, the applicability must be rigorously verified within the laboratory before implementation. The purpose of this study is to demonstrate comprehensive validation, necessary modification, and subsequent evaluation of auto verification rules to confirm their fitness for clinical application.**

Methods: **Auto verification rules were configured within a middleware system (laboratory data management software linking analyzers and laboratory information system) integrated into laboratory information system (LIS, a clinical lab data management system) at Peking University First Hospital and subsequently executed. A total of four rounds of validation were conducted using outpatient coagulation test results from March 2023 to March 2024. We analyzed the auto verification pass rate, the correct application of verification markers for all samples, and compared the outcomes with those of manual verification performance metrics, including the auto verification pass rate, true positive rate (TPR), true negative rate (TNR), false positive rate (FPR), false negative rate (FNR), and the impact on turn-around-time (TAT), were calculated.**

Results: **Following four rounds of iterative modifications, the auto verification system achieved a pass rate of 69.70%. The performance metrics demonstrated 100% true positive rate (TPR) and 0% false negative rate (FNR), alongside a true negative rate (TNR) of 67.93% and a false positive rate (FPR) of 32.07%. Consequently, the median TAT decreased significantly from 80.0 minutes to 63.1 minutes (p = 0.001).**

Conclusions: **This study comprehensively describes the validation and modification process of auto verification rules for coagulation tests based on the Werfen coagulation system. Furthermore, this study establishes a framework and provides a practical methodology for implementing auto verification in clinical laboratories.**

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Correspondence:
Chenxue Qu
Department of Clinical Laboratory
Peking University First Hospital
Beijing
China
Email: qucx2012@163.com

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KEYWORDS

auto verification rules, coagulation tests, rule validation

LIST OF ABBREVIATIONS

APTT - activated partial thromboplastin time
PT - prothrombin time
INR - international normalized ratio
TT - thrombin time
Fib-C - fibrinogen Clauss method
D-D - D-dimer
FDP - fibrin/fibrinogen degradation products

LIS - laboratory information system
TAT - turn-around-time
QC - quality control
LOD - limit of detection
TPR/TNR/FPR/FNR - true positive/true negative/false positive/false negative rate
CLSI - Clinical and Laboratory Standards Institute

INTRODUCTION

Auto verification refers to a fully automated, rule-driven process for clinical laboratory testing that validates and releases analytical results without manual intervention by laboratory personnel. The increasing workload in clinical laboratories has necessitated the adoption of auto verification, implemented within the Laboratory Information Systems (LIS) or middleware, to ensure reporting efficiency [1]. Particularly critical for coagulation testing is shortening the turn-around-time (TAT) for the timely diagnosis and treatment of patients with bleeding and thrombosis disorders. While our previous multicenter study established a set of detailed auto verification rules for routine coagulation tests [2], their suitability for our laboratory requires local validation and potential adjustment. Therefore, this study aims to provide a comprehensive demonstration of the validation and evaluation process necessary prior to the application of the auto verification rules.

MATERIALS AND METHODS

Materials

Data for auto verification rules

A total of 18,602 outpatient coagulation samples from Peking University First Hospital collected between March 2023 and March 2024 were used.

Instruments and Reagents

ACL TOP 750 LAS Coagulation System with Activated Partial Thromboplastin Time (APTT), Prothrombin Time (PT), Thrombin Time (TT), Fibrinogen Clauss method (Fib-C), D-Dimer (D-D), Fibrin Degradation Products (FDP) reagents, calibrators, and quality controls were used.

Establishment and selection of auto verification rules

Following the Clinical and Laboratory Standards Institute (CLSI) Guideline AUTO 10-A [3] and AUTO 15 [4], we previously established a set of auto verification rules and a corresponding flow chart as presented in Figure 1. The selection of auto verification rules should also be accounted for the functionality of the laboratory information system and its interfacing capability with the middleware.

Validation and evaluation of auto verification rules

The auto verification rules were implemented within a middleware system (HemoHub), which was integrated into LIS. The LIS sent patient data, including age, gender, department, medication, and historical results to HemoHub for rule-based auto verification assessment. HemoHub returned a pass/fail flag back to the LIS.

Initial Validation (First-round)

In the first-round validation, coagulation test results from March to April 2023 were utilized. The objectives were to assess the auto verification pass rate and to confirm the correct application of verification flags for all samples. The rules were subsequently adjusted based on these findings.

Secondary Validation (Second-round and Third-round)

This subsequent phase of validation utilized coagulation test results from May to December 2023. The rules were further refined based on the observed pass rates to enhance performance.

Final Validation (Fourth-round)

Upon finalizing the rules, a validation was conducted using coagulation test results from January to March 2024 to assess human-machine consistency verification. The auto verification process was executed in the clinical laboratory, and all results underwent a concurrent manual review by experienced laboratory technicians. The verification pass rates of auto verification and manual verification were compared, and the performance of the auto verification rules was comprehensively evaluated by calculating the overall pass rate, true negative rate (TNR), true positive rate (TPR), false negative rate (FNR), and false positive rate (FPR).

Efficiency Assessment

The efficiency of auto verification was assessed by turn-around-time (from specimen receipt to result verification) against that of manual verification. A statistical analysis was performed to determine if a significant difference existed.

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics Version 25.0 (IBM SPSS Statistics for Windows; IBM Corp., Armonk, NY, USA). The difference in TAT between auto verification and manual verification was analyzed using the Mann-Whitney U test for independent samples, with a 95% confidence interval. A $p < 0.05$ was considered statistically significant.

RESULTS

Establishment and selection of auto verification rules

The auto verification rules were implemented based on the flowchart established in our previous study as presented in Figure 1. However, minor adjustments were required to optimize their performance within the specific operational context of our laboratory.

Table 1. Test results distribution.

	n	Mean	SD	Median	Range	Minimum	Maximum	Percentiles	
								5%	95%
PT (second)	1,227	13.04	4.35	11.90	80.20	9.00	89.20	10.50	19.90
APTT (second)	1,128	33.65	5.39	32.90	59.70	23.60	83.30	27.60	41.60
TT (second)	1,118	14.81	8.11	14.10	194.30	10.30	204.60	12.40	17.70
Fib-C (g/L)	1,147	3.11	1.00	2.97	9.11	0.13	9.24	1.77	4.76
D-D (mg/L)	724	1.36	3.79	0.31	63.20	0.00	63.20	0.02	6.14
FDP (mg/L)	671	11.85	31.87	2.90	550.50	0.00	550.50	0.36	54.62

Table 2. Reference range, Limit of Detection (LOD), the results distribution range of 5% - 95%, and Limit Range.

	Reference range	LOD	The results distribution range of 5% - 95%	Limit range
PT	10.10 - 12.60 second		10.50 - 19.90 second	10.10 - 19.90 second
APTT	26.90 - 37.60 second		27.60 - 41.60 second	26.90 - 41.60 second
TT	12.50 - 16.50 second		12.40 - 17.70 second	12.40 - 17.70 second
Fib-C	2.00 - 4.00 g/L	0.35 g/L	1.77 - 4.76 g/L	1.77 - 4.76 g/L
D-D	0.00 - 0.24 mg/L	0.02 mg/L	0.02 - 6.14 mg/L	0.02 - 6.14 mg/L
FDP	0.00 - 5.00 mg/L	1.0 mg/L	0.36 - 54.62 mg/L	0.00 - 54.62 mg/L

Table 3. Overall pass rate, individual pass rates for each assay in the first-round validation.

Metrix	APTT	PT	FIB	TT	D-D	FDP	Total Samples
Passed (No.)	1,425	1,362	1,298	1,307	340	11	1,262
Total (No.)	1,515	1,440	1,343	1,339	378	63	1,733
Pass Rate (%)	94.06%	94.58%	96.65%	97.61%	89.95%	17.46%	72.82%

Table 4. Overall pass rate, individual pass rates for each assay in the second-round validation.

Metrix	APTT	PT	FIB	TT	D-D	FDP	Total Samples
Passed (No.)	1,590	1,452	1,499	1,493	563	212	1,119
Total (No.)	1,723	1,661	1,551	1,523	585	460	1,997
Pass Rate (%)	92.3%	87.4%	96.6%	98.0%	96.2%	46.09%	56.03%

Table 5. Overall pass rate, individual pass rates for each assay in the third-round validation.

Metrix	PT	APTT	FIB	TT	D-D	FDP	Total Samples
Passed (No.)	3,484	3,701	3,433	3,389	1,049	479	2,533
Total (No.)	3,790	3,955	3,508	3,455	1,371	1,047	4,488
Pass Rate (%)	91.93%	93.58%	97.86%	98.09%	76.51%	45.75%	56.44%

Table 6. Overall pass rate, individual pass rates for each assay in the fourth-round validation.

Metrix	PT	APTT	FIB	TT	D-D	FDP	Total Samples
Passed (No.)	8,299	8,587	8,116	7,996	2,276	2,268	7,238
Total (No.)	8,962	9,185	8,359	8,211	3,007	2,348	10,384
Pass Rate (%)	92.60%	93.49%	97.09%	97.38%	75.69%	96.60%	69.70%

Table 7. Concordance between auto verification and manual verification for sample results in the fourth-round validation.

	Manual verification failed	Manual verification passed	Total
Auto verification failed	3,146	2,321	5,467
Auto verification passed	0	4,917	4,917
Total	3,146	7,238	10,384

General auto verification rules

The following criteria were evaluated for all samples before initiating the auto verification process: QC status, test assays match the order or not, results' numerical format, and alarm information.

Critical Value Criteria

Test results exceeding the predefined critical values were referred to as manual verification. The critical values in our laboratory are defined as follows: APTT > 60 seconds, PT > 20 seconds, International Normalized Ratio (INR) > 5, FIB-C < 1 g/L (obstetrics < 2 g/L), and D-D > 4 mg/L.

Delta Check

The delta check rules were implemented as established [2]. Utilizing the following thresholds: APTT < 6.41 seconds; PT < 3.95 seconds; FIB-C < 0.97 g/L; TT < 4.03 seconds; D-D < 1.81 mg/L; FDP < 12.42 mg/L.

Limit range

The 95% confidence intervals for the test limit ranges were calculated using local data (as shown in Table 1), after excluding samples from patients on anticoagulants, those with suboptimal quality, or those triggering alarms. Subsequently, the final verification range for each test was established based on its analytical measurement range as well as the clinical reference interval (as shown in Table 2).

For special populations, including obstetrics and elderly patients (age > 60), the limit ranges established in our previous study were directly applied [2].

Enlarge limit range with certain conditions

A technical constraint prevented the transmission of patient surgery and medication information from the LIS to HemoHub. Consequently, this ruled out the feasibility of implementing context-dependent limit ranges in this study.

Logical check

We adopted the logical check rules from our prior study without modification [2].

Evaluation and revision of auto verification rules

An initial validation was performed using sample results from March to April 2023. The overall pass rate and the individual pass rates for each assay are shown in Table 3.

A low sample volume was observed for FDP and D-D in the initial round of validation. Investigation revealed that samples with specific result patterns were not captured by the initial rule, subsequently leading to their exclusion. To address this, 2 additional logical rules were added for revision. 1) D-D ≤ 0.24 mg/L and FDP > 5 mg/L, 2) D-D > 0.5 mg/L and FDP < 5 mg/L.

The second-round validation was performed using sample results from May to August 2023. The overall pass rate and the individual pass rates for each assay are shown in Table 4.

The second-round evaluation indicated an unusually high pass rate for D-Dimer. Investigation revealed that a substantial proportion of D-Dimer tests lacked historical data or concurrent FDP results for logical check. An excessively wide limit range, while increasing the pass rate, could elevate the risk of false positives due to interferents like rheumatoid factors. To mitigate this risk while maintaining safety, the lower limit range for D-D was constrained. The rule was adjusted as follows: for samples lacking both historical data and a concurrent FDP result, the biological reference interval of 0.02 - 0.24 mg/L was applied as the verification limit. The third-round validation was performed using sample results from September to December 2023. The overall pass rate and the individual pass rates for each assay are shown in Table 5.

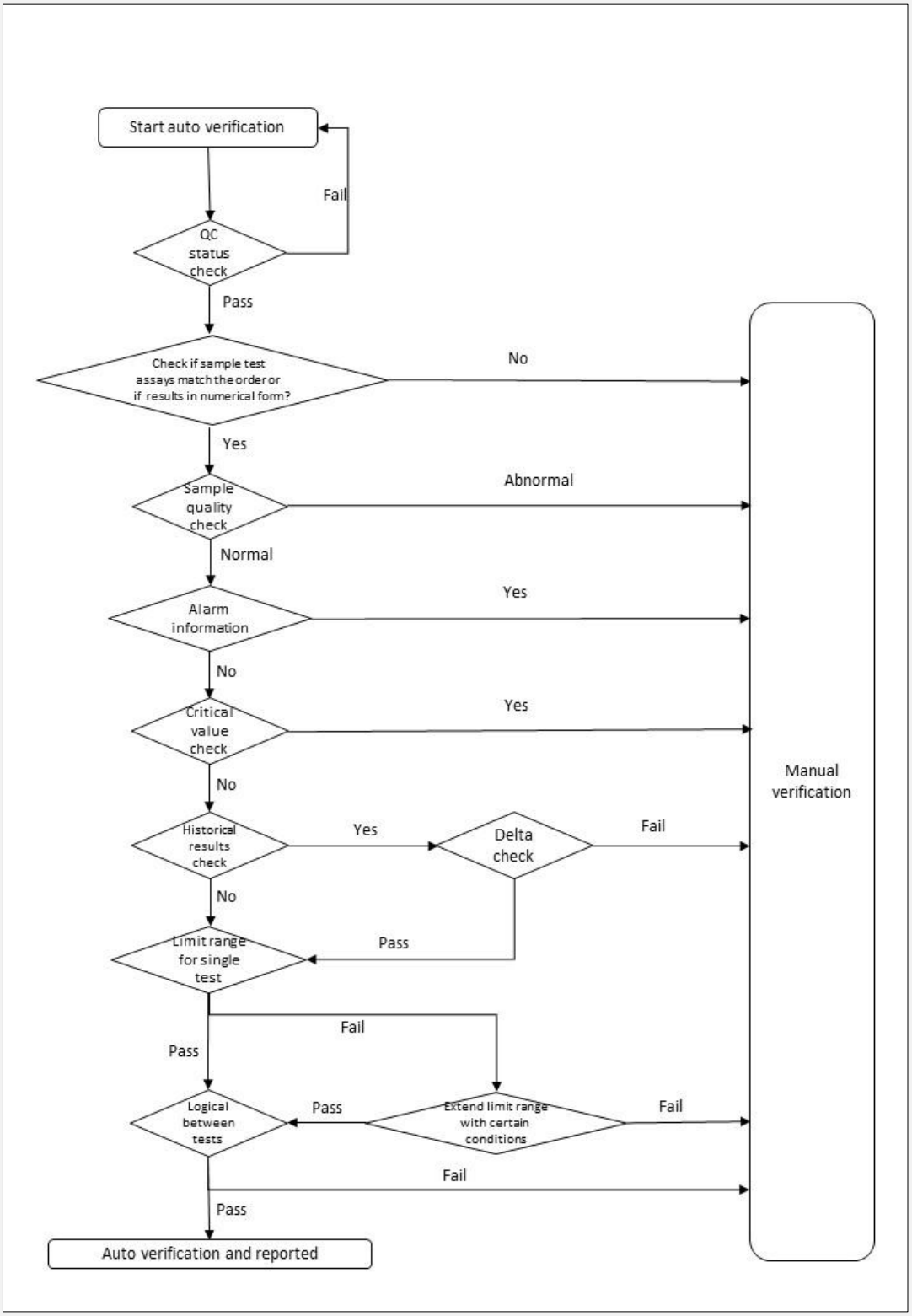

Figure 1. Workflow chart of auto verification.

This figure is adapted from Miao L, et al. Informatics in Medicine Unlocked, Volume 32, 2022, https://doi.org/10.1016/j.imu.2022.101019, CC BY 4.0. Changes were made [2].

From the third-round evaluation, the pass rate for FDP was unexpectedly low. An investigation revealed that this was attributable to the lower limit of 1.00 mg/L, a threshold that lacked clinical utility. Consequently, the lower limit was adjusted to 0 mg/L to improve pass rates without compromising clinical safety.

The fourth-round validation was performed using sample results from January to March 2024. The overall pass rate and the individual pass rates for each assay are shown in Table 6.

During the final validation phase, the overall pass rate for auto verification was 69.70%. The true negative rate (TNR), true positive rate (TPR), false-negative rate (FNR), and false-positive rate (FPR) of the auto verification rules were evaluated with the following algorithms:

$$\text{True positive rate} = \frac{\text{number of sample results did not pass manual verification and auto verification}}{\text{number of sample results did not pass manual verification}} \times 100\%$$

$$\text{True negative rate} = \frac{\text{number of sample results pass manual verification and auto verification}}{\text{number of sample results pass manual verification}} \times 100\%$$

$$\text{False positive rate} = \frac{\text{number of sample results did not pass auto verification but pass manual verification}}{\text{number of sample results pass manual verification}} \times 100\%$$

$$\text{False negative rate} = \frac{\text{number of sample results pass auto verification but did not pass manual verification}}{\text{number of sample results did not pass manual verification}} \times 100\%$$

The concordance between automated and manual verification outcomes is illustrated in Table 7. The human-machine consistency analysis of these results demonstrated a TPR of 100% and a FNR of 0%. In addition, a true negative rate (TNR) was 67.93% and a false positive rate (FPR) was 32.07%.

Efficiency assessment of auto verification rules

Coagulation test data of 10,384 samples from January to March 2024 in the fourth-round validation were used for the efficiency assessment of auto verification. The TAT for auto verification and manual verification were both assessed using these data. TAT for auto verification was 63.1 (52.2 - 83.5) minutes. TAT for manual verification was 80.0 (62.3 - 119.2) minutes. The median TAT for auto verification was significantly lower than that for manual verification, this reduction was a statistically significant difference ($p = 0.001$).

DISCUSSION

Prior to implementation in a clinical laboratory, auto verification rules must undergo rigorous validation. Initially, each laboratory should configure the rule criteria based on local data and in alignment with the established principles for rule development. For example, each laboratory should define critical value according to its specific operational context. Furthermore, the review of historical results is very crucial, as it can reveal significant trends in a patient's condition and help identify potential analytical errors. For samples with historical results, the review of historical results should be performed as a primary step [5,6]. When establishing delta check rules, the criteria for each test should be tailored to the specific conditions of the individual laboratory. For instance, in settings where patient conditions can change rapidly, such as cardiovascular laboratories and emergency centers, the review period should be optimized by using a shorter historical period, for example, 3 days or 7 days. The reportable range for each test can be established by integrating the 95% confidence interval with lower detection limit and biological reference interval [2]. Concurrently, the laboratory should fully consider the age and physiological state of its patient population in the laboratory and establish criteria for each specific limit accordingly [2]. Laboratories can define the extended reporting range based on their specific clinical requirements and the interoperability between the laboratory information system and the middleware (HemoHub). For logical checks, rules established in prior research can be applied, such as the correlation between D-Dimer and FDP. Furthermore, additional logical rules may be incorporated based on the analysis of abnormal results identified during manual verification. It is imperative that auto verification rules undergo repeated validation and adjustment after their configuration and prior implementation. ISO 15189:2022 mandates that medical laboratories validate auto verification rules for routine coagulation tests as part of their risk-based quality management systems. The standard also requires regular review and refinement of these rules to adapt to ensure patient safety and support continuous improvement in post-analytical workflow efficiency [7]. In recent years, large-scale clinical data have shown that after validation and subsequent implementation, the auto verification system for coagulation tests can further shorten the turn-around-time (TAT) with no false-negative results [8,9]. However, no further rigorous validation research on auto verification rules has been performed in these studies to explore the applicability and verification efficiency of each separate rule, a critical step to further safeguard clinical safety and enhance the overall pass rate. In this study, four rounds of systemat-

ic validation were conducted. The validation process involved detailed analysis of both the pass rate for individual auto verification rules and the comprehensive flagging of all samples within the system. A critical consideration in this process is ensuring complete coverage of all test results by the auto verification framework. Due to the deterministic nature of computational logic, certain test results may fall outside predefined rules. Consequently, they may bypass automated verification and fail to generate appropriate flags within the laboratory information system. In configurations where the default system behavior permits unreviewed release of non-flagged results, a significant risk emerges wherein unverified test data may be inadvertently disseminated. To mitigate this risk, each round of validation should incorporate two essential validation procedures: one is to check the flag distribution across all test results to confirm complete coverage, coupled with systematic evaluation of rule comprehensiveness for each analytical parameter; and secondary, confirm that the laboratory information system automatically designates non-flagged results as "blocked" rather than permitting their uncontrolled release. For example, initial validation in this study, we found revealed coverage gaps in D-Dimer and FDP limit ranges, allowing certain results to evade automated review. Furthermore, the initial rule set lacked logical validation for discordant results between D-D and FDP. To address these deficiencies, additional logical rules were added for revision, establishing blocking criteria for physiologically implausible correlations between D-D and FDP (if D-D $\leq$ 0.24 mg/L and FDP > 5 mg/L, or D-D > 0.5 mg/L and FDP < 5 mg/L).

During validation of auto verification rules, it is essential to analyze the passing rate of blocking causes for each test assay. Assays with low pass rate should be identified, their blocking reasons thoroughly investigated, and appropriate adjustments made without introducing additional clinical risks. For example, during the third-round validation, the overall passing rate was initially only 56.44%, primarily due to the suboptimal pass rate of FDP. Further analysis showed that elevated blocking rate for FDP was largely attributable to its lower reporting limit being set at 1. After adjusting the lower limit to 0, the pass rate for FDP improved significantly, leading to a corresponding increase in the overall pass rate. Moreover, no false negative results were observed either before or after the rule modifications. However, it is crucial to recognize that an excessive pursuit of a high pass rate may increase of false negative; therefore, clinical risks must be thoroughly evaluated when adjusting rules.

After four rounds of validation, the overall auto verification pass rate reached 69.70%, a figure slightly lower than some earlier studies [10,11]. This discrepancy is potentially attributable to the use of a dataset derived from a large general hospital, where patient populations and clinical conditions are typically more complex. Additionally, the stringent criteria employed in the present study may have contributed to the more conservative pass rate. Nevertheless, the implementation of auto verification significantly reduced the median TAT from 80.0 minutes to 63.1 minute, which is consistent with existing literature [10,11], confirming the efficacy of such rules in enhancing operational efficiency.

Our study has some limitations. First, the data was exclusively limited to outpatient samples, which may restrict the generalizability to inpatient or emergency department settings. Second, the middleware system did not receive data about medication and surgery. So, we did not set the extend limit range for these special conditions affecting coagulation results in auto verification rules, which can increase the passing rate within reasonable limits. Consequently, these constraints should be carefully considered when extrapolating the results to broader clinical contexts or more comprehensive data streams.

CONCLUSION

This study demonstrates a comprehensive framework for the auto validation and necessary modification process of auto verification rules for coagulation tests based on Werfen coagulation system. The implemented strategy provides a validated methodology for clinical laboratories to adopt auto verification, thereby significantly enhancing operational efficiency through a reduced turn-around-time (TAT).

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