Review

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Recent advances in laboratory hematology reflected by a decade of *CCLM* publications

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Abstract: On the occasion of the 60th anniversary of *Clinical Chemistry and Laboratory Medicine* (*CCLM*) we present a review of recent developments in the discipline of laboratory hematology as these are reflected by papers published in *CCLM* in the period 2012–2022. Since data on *CCLM* publications from 1963 to 2012 are also available, we were able to make a comparison between the two periods. This interestingly revealed that the share of laboratory hematology papers has steadily increased and reached now 16% of all papers published in *CCLM*. It also became evident that blood coagulation and fibrinolysis, erythrocytes, platelets and instrument and method evaluation constituted the 'hottest' topics with regard to number of publications. Some traditional, characteristic *CCLM* categories like reference intervals, standardization and harmonization, were more stable and probably will remain so in the future. With the advent of important newer topics, like new coagulation assays and drugs and cell population data generated by hematology analyzers, laboratory hematology is anticipated to remain a significant discipline in *CCLM* publications.

Keywords: 60 years *CCLM*; laboratory hematology; publications; review.

Introduction

When *Clinical Chemistry and Laboratory Medicine* (*CCLM*) was launched in 1963 under the name '*Zeitschrift für Klinische Chemie*', it was entirely devoted to clinical chemistry in the strict sense. The first paper that currently is regarded as belonging to the domain of laboratory hematology appeared in 1966 [1]. With the expansion of the journal, not only the number of published papers steadily increased, also the share of papers on laboratory hematology subjects has risen, to approximately 10% in 2012 [2]. And this upward trend has continued until present, since during the 6th decade of *CCLM's* existence, almost 16% of all published papers were in the domain of laboratory hematology. The journal's 60th anniversary is a good moment to review recent developments in laboratory hematology, their impact on *CCLM* publications and indirectly their impact on patient care. This review is focused on a number of selected subjects, where *CCLM* has played a key role in developing the area of interest or which are otherwise characteristic for the journal.

Materials and methods

For the current review we have used the same definitions for laboratory hematology as in a previous overview in order to enable comparisons with the first 50 years of *CCLM* [2]. Included in the field are the categories given in Table 1, while excluded were papers on iron metabolism, blood gas analysis, glycated Hb, monoclonal gammopathy, vitamin B_{12}, folate and homocysteine. Search strategy, categorization and citation analysis were also identical to the previous report [2]. Analyses included the July 2012 until the June 2022 issues of the journal.

Results and discussion

In its 6th decade, *CCLM* published 594 papers on laboratory hematology subjects (Table 1), which is over 1½ times the amount achieved in the 5 decades before (387), implying a very significant increase. As the journal published 3,733 papers over the last 10 years, also the relative amount of laboratory hematology papers rose to an impressive 15.9%. The steady increase that was observed over the first 50 years (see Figure 1 in [2]) clearly continued in the last decade. This reflects the increasing importance of laboratory hematology within the wide field of laboratory medicine. Factors that undoubtedly play a role here are the progressing level of automation, including the availability of new research parameters, a shift of molecular diagnostics from research to routine settings and,

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Table 1: Numbers of papers in the domain of laboratory hematology published in *CCLM* between 2012 and 2022, compared with the journal's first 50 years 1963–2012.

Category	2012–2022	1963–2012
Biological variability	10 (1.7%)	4 (1.0%)
Blood cell isolation	1 (0.2%)	2 (0.5%)
Blood cell morphology	20 (3.4%)	2 (0.5%)
Blood transfusion	9 (1.5%)	5 (1.3%)
Cell population data	12 (2.0%)	–
Cells in body fluids and bone marrow	12 (2.0%)	6 (1.6%)
Cellular immunology	5 (0.8%)	4 (1.0%)
Coagulation and fibrinolysis	151 (25.4%)	91 (23.5%)
Covid-19	23 (3.9%)	–
Cytokines and growth factors	0 (0.0%)	17 (4.4%)
Doping	0 (0.0%)	7 (1.8%)
Eosinophils	0 (0.0%)	4 (1.0%)
Erythroblasts	4 (0.7%)	7 (1.8%)
Erythrocyte sedimentation rate	3 (0.5%)	11 (2.8%)
Erythrocytes and RBC parameters	40 (6.7%)	13 (3.4%)
Flow cytometry	6 (1.0%)	6 (1.6%)
Hemoglobin and hematocrit	9 (1.5%)	22 (5.7%)
Hemoglobinopathy	48 (8.1%)	20 (5.2%)
Infection, inflammation and sepsis	16 (2.7%)	9 (2.3%)
Instrument and method evaluation	44 (7.4%)	28 (7.2%)
Leukocytes	21 (3.5%)	15 (3.9%)
Lymphocytes	8 (1.3%)	3 (0.8%)
Molecular diagnostics	19 (3.2%)	19 (4.9%)
Platelet count and platelet function	42 (7.1%)	27 (7.0%)
Pre-analytical phase	24 (4.0%)	22 (5.7%)
Quality control	25 (4.2%)	17 (4.4%)
Reference values	18 (3.0%)	9 (2.3%)
Reticulocytes	2 (0.3%)	12 (3.1%)
Standardization, harmonization	14 (2.4%)	5 (1.3%)
Various	8 (1.3%)	–
All	**594** (100.0%)	**387** (100.0%)

last but not least, a higher degree of professionalism among clinical laboratory specialists due to improved education and specialization in hematology. Or in other words, laboratory hematology continues maturing as a discipline, next to and separate from traditional clinical chemistry.

When comparing the subjects addressed in these two periods they show much similarity, but some striking differences can be noted (Table 1). In recent years, no papers were published on cytokines and growth factors, doping and eosinophils. New categories were cell population data (CPD) from hematology analyzers and of course Covid-19. Categories that showed an evident increase in relative occurrence were blood cell morphology, erythrocytes and hemoglobinopathy. The most popular field remained coagulation and fibrinolysis with the relative contribution more or less constant. Also the characteristic *CCLM* subjects like quality control and reference values appeared to be relatively stable. The most notable topics will be discussed in detail below.

Blood cell morphology

At first sight it might seem a bit remarkable that the number of papers on blood cell morphology increased, now we are living in the era of laboratory automation. Yet, this growth becomes understandable when one reads the papers and sees that many of them were initiated by an alert or abnormal scatter pattern in the hematology analyzer, which prompted further microscopic examination [3, 4]. In the past, when hematology analyzers had a lower level of technological sophistication, some of these cases undoubtedly would have gone unnoticed and never led to a publication.

Cell population data

A relatively new topic in the literature is cell population data (CPD). These are actually the raw measurement signals produced by modern hematology analyzers for every single white blood cell (WBC) analyzed. In hematology analyzers with multiple detectors, every leukocyte generates a set of signals, which the software uses for characterizing the cell. Once the various WBC populations are defined, the mean and dispersion of all signals in each cell population is calculated. Actually, a set of CPD can be regarded as the fingerprint of a patient's WBC at a given moment and CPD harbor information that is directly or indirectly associated with cell morphology. For example, neutrophil volume is increased in case of immature granulocytes in blood, toxic granulation may increase the neutrophil side scatter signal (granularity), while viral infection can be associated with increased lymphocyte volume.

CPD were first accessible in the Beckman Coulter LH750 analyzer and some neutrophil CPD appeared to be useful indicators of acute bacterial infection [5]. Later this observation was extended to lymphocyte parameters and used for characterizing the malignant cells of chronic lymphatic leukemia and myelodysplastic syndrome [6]. Another early *CCLM* paper reported neutrophil CPD for defining asthma phenotypes in an Abbott hematology analyzer [7]. Over the next years, CPD were made available in more analyzer brands [8–10] and the number of disease states where neutrophil CPD are considered useful nowadays includes neonatal and adult sepsis [8, 11–13], postoperative infection [14], tuberculosis [15], myelodysplastic syndrome [16, 17], acute and chronic leukemia [18–20] and transplant engraftment [21, 22]. Lymphocyte CPD can provide additional information in viral infection [23], lymphocytosis [24–26] and tropical infections like dengue [27, 28]. The significance of monocyte CPD was boosted by the Covid-19 pandemic, as monocyte volume distribution width (MDW) was found to have prognostic value

for Covid-19 severity [29–33] and MDW also appeared to be an early indicator of sepsis in general [32, 34–36]. From these references it is clear that *CCLM* played an important role in disseminating information on MDW.

In spite of the positive findings of CPD in a variety of clinical conditions, most authors seem to have overlooked the potential drawbacks of CPD and their analysis. Firstly, CPD values are sensitive to preanalytical storage conditions [37]. Further, they are specific for a certain hematology analyzer and even analyzers of the same type do show variation in CPD [38]. This is because the raw measurement signals depend on the individual optical and electronic components in the analyzer and their exact alignment in the optical bench. Thus, CPD are not only the fingerprint of a specific blood sample, but of a blood sample in combination with an individual hematology analyzer. CPD can be harmonized between different analyzers only by optical adjustments [38]. Practically all studies on the clinical utility of CPD were performed on a single hematology analyzer and this constitutes a serious limitation for applying the findings to other analyzers. Moreover, there are no data as yet on the long-term stability of CPD measured with a single or multiple analyzers. In this respect, the practical usefulness of CPD reference intervals is questionable and they need to be prudently interpreted [39, 40].

Coagulation and fibrinolysis

With approximately one quarter of all laboratory hematology papers in *CCLM*, this category continues to play the main role. Obviously, the subjects are now different from the past, reflecting the progress in diagnostic tests and drugs development. Major topics in the past 10 years include lupus anticoagulant and the antiphospholipid syndrome [41–45], congenital thrombophilia testing [46–49], the new direct oral anticoagulants [50–56] and D-dimer, most recently as an indicator of the intravascular coagulation associated with severe COVID-19 disease [57–60]. Apart from original research, the journal also published discussion papers that highlight pros and cons, helping the readers forming their own opinion on the subject [44–48].

Covid-19

Obviously, SARS-CoV-2 and Covid-19 are new topics for all biomedical journals. In a period of 2.5 years the scientific community produced an impressive total of nearly 280,000 papers on the virus and the disease (PubMed search, accessed 23 September 2022). The contribution of *CCLM* was quite moderate with a total of 195 papers, of which we classified 23 in the laboratory hematology domain (Table 1). Notable Covid-19 related subjects were coagulation (D-dimer, thrombin formation) and the CPD mentioned above. Despite this modest number of publications, their impact was very impressive, judging by the high citation rates of some of them (see below).

Erythrocytes: RDW

Red cell distribution width (RDW) is a quantitative measure of red blood cell (RBC) heterogeneity. The concept was developed by Cecil Price-Jones, who measured the diameter of RBC in blood smears using a calibrated eyepiece in a microscope [61]. The RBC distribution was useful to differentiate between pernicious anemia and anemia after blood loss, but his method was too cumbersome and time-consuming to gain widespread practical use. After Wallace Coulter had applied electrical impedance measurement for counting blood cells in suspension, it became possible to determine RDW, now defined as the dispersion of RBC volume. Since the 1980's most hematology analyzers are able to report RDW, albeit that the parameter is not standardized and thus varies between analyzers and technologies [62, 63]. RDW is traditionally expressed as the coefficient of variation of the RBC volume histogram (RDW-CV), making the RDW MCV-dependent. For example, increased RDW can be obscured by increased MCV. Therefore, expressing RDW in absolute volume units (RDW-SD) is to be preferred, as it is MCV-independent. Some modern hematology analyzers do report RDW-SD along with RDW-CV and indeed, there are indications that the utility of RDW-SD exceeds that of RDW-CV [64–67].

Initially RDW was used as a diagnostic tool in anemia workup and the yearly number of publications mentioning RDW was less than 300 (Figure 1). In 2007, Felker and colleagues published their paper on RDW as an independent prognostic marker in heart failure [68] and this report stimulated other researchers examining RDW as a risk indicator in a large variety of disorders. As a consequence, the number of papers on RDW has dramatically increased: in the last few years, over 1,000 papers on RDW are published annually (Figure 1). Increased RDW has been statistically associated not only with cardiovascular events, but also with cancer, acute illnesses, ischemic stroke, kidney disease, pulmonary hypertension, mortality from community-acquired pneumonia, Behçet's disease, post-surgery mortality, thromboembolic disorders, migraine attacks, Covid-19 and numerous other diseases. In all these conditions RDW reflects erythropoietic dynamics in response to anemia or inflammatory

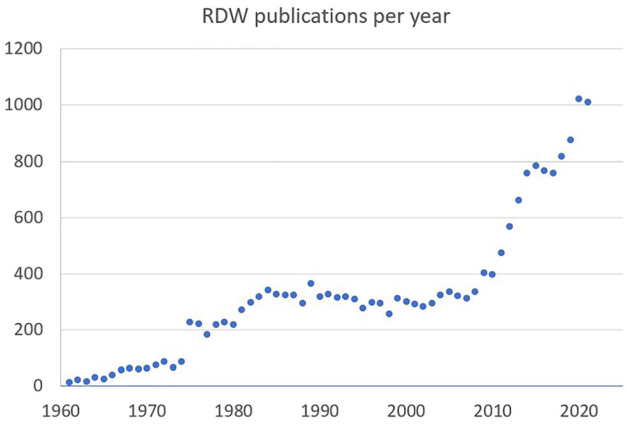

Figure 1: Number of all publications on RDW per year since 1960 (source: PubMed).

stimuli [69]. So, just like the erythrocyte sedimentation rate, RDW is a fully non-specific marker of inflammation, with some prognostic value for highly diverse situations.

Apart from some papers on RDW as a prognostic marker, *CCLM* has published papers on RDW reference intervals [70–72] and biological variation [73, 74], which are important for correct interpretation.

Erythrocytes: discriminant functions in microcytic anemias

Over the years, many discriminant formulas have been developed for the differential diagnosis of microcytic anemia. Nearly all of these formulas include basic hematology parameters only, which are available on all hematology analyzers, including the less sophisticated ones. Many evaluation studies on the performance of these discriminant formulas have been published, but most of them were on small patient cohorts, not independently validated and the results are rather contradictory. We have undertaken a retrospective study using a large database of well-characterized individuals with microcytic anemia and compared the 25 most frequently used formulas [75]. We could identify three formulas with superior sensitivity and specificity: the Green & King, Jayabose and Janel 11T score, demonstrating that complex mathematical formulas are not necessary for screening purposes. Notably, all these three high-performance formulas include RDW, suggesting that this is a critical parameter for distinguishing between iron deficiency anemia and thalassemia trait. And as mentioned above, using the RDW-SD gives even better results than the RDW-CV [65, 76]. However, despite their good performance for screening, the diagnostic utility of even the best formulas remains insufficient for basing a final thalassemia diagnosis on [75].

Erythrocytes: microcytic and hypochromic cells

Fundamental research on optical characteristics of blood cells made it possible to accurately measure RBC volume and refractive index (representing cellular hemoglobin content), using flow cytometry, based on the Mie principle of light scattering [77]. The Technicon company (later Bayer, now Siemens) was the first to apply this principle in a hematology analyzer [78]. Later this or similar technology was made available in other hematology analyzers, enabling the enumeration of microcytic, macrocytic, hypochromic and hyperchromic RBC [79]. We were able to demonstrate that the ratio of microcytic and hypochromic RBC (the M/H ratio) was a highly useful tool for the differential diagnosis between iron deficiency anemia and β-thalassemia trait in persons with microcytic anemia [80, 81]. Later *CCLM* published a meta-analysis, confirming the superior performance of the M/H ratio for distinguishing these conditions [82].

Platelet count and platelet function: reticulated platelets

Just like reticulocytes provide information on the erythropoietic activity in bone marrow, reticulated platelets do that for megakaryopoiesis. Until the late 1990s flow cytometry was the only technique for measuring reticulated or immature platelets, obviously impeding clinical use. The TOA (now Sysmex) R-3000 reticulocyte analyzer was the first with the capacity to enumerate reticulated platelets [83]. This parameter was shown to be mainly useful for the differential diagnosis of thrombocytopenia: reduced thrombopoiesis vs. increased platelet turnover. Nowadays, reticulated or immature platelets analysis is integrated in some high-end automated hematology analyzers and patients with thrombocytopenia can benefit from their measurement [84–86]. Papers devoted to (pre-)analytical aspects of reticulated platelets are available thanks to *CCLM*, too [85, 87, 88].

Hemoglobinopathy

The number of *CCLM* papers on hemoglobinopathy has significantly increased over the last 10 years, both in

absolute and relative sense (Table 1). This can be mainly attributed to two factors: the growth in use of automated HbA_{1c} analyzers and the increase in the technological level of hematology analyzers. As a laboratory journal, *CCLM* has become an important forum for reporting known or newly discovered Hb variants that interfere with HbA_{1c} measurement on one or more HbA_{1c} analyzers, as some selected examples demonstrate [89–93]. Additional peaks, sometimes overlapping with the normal Hb peaks, are generally a sign that an abnormal Hb may be present and that additional investigations are necessary.

Another source of detection of Hb variants is the hematology analyzer that produces abnormal scatterplots in one of more channels. The phenomenon of an abnormal Hb variant incidentally detected in a hematology analyzer was first described in a patient with Hb-Köln, presenting as pseudo-reticulocytosis in the Abbott Cell-Dyn 4000 analyzer [94]. All other reports are more recent and *CCLM* has published the majority of them [95–101], including findings of Hb M Dothan [97], Hb Leiden [95, 99] and Hb Mozhaisk [100]. All but one cases were found during analysis with Sysmex XE- or XN-analyzers, presenting as lowered fluorescence intensity of the WBC in the DIFF or WDF scattergrams, respectively. Recently, the Urrechaga group reported in this journal the first case of abnormal Hb incidentally detected in a Mindray BC-6800 hematology analyzer, namely Hb Johnstown [101]. A second report in a Mindray BC-6800 identified Hb Shelby, giving comparable abnormal scattergrams [102]. These three analyzers use highly similar reagents for the WBC differential and a plausible hypothesis is that the abnormal Hb released from lysed RBC binds the fluorescent dye with high affinity, so that there is insufficient dye left for staining the nucleated cells, resulting in the low or very low fluorescence signal in the scattergrams [95–97]. Alternatively, the low signals might be explained by fluorescence quenching due to the abnormal Hb or RBC ghosts [98]. Currently, no other hematology analyzer types than the three mentioned above have been reported to be associated with incidental abnormal Hb variants, strongly suggesting that the phenomenon is reagent-specific.

Instrument and method evaluation

The relative share of *CCLM* publications in this category has remained stable (Table 1) and the papers do reflect the development and introduction of new analyzers by the various manufacturers. Not surprisingly, papers on hematology analyzers are the most frequent in this category, approximately 80%, and the number of papers roughly represent the market shares of the main manufacturers. Some papers are of direct practical interest for the journal's readers: early evaluation reports of newly released analyzer models [103–105], side-by-side comparison studies of various analyzers [84, 106–108] and case reports on interfering factors that compromise the accuracy of reported results [98, 109–112]. A critical paper on unreliable basophil counts reported by hematology analyzers belongs to this group, too [113]. Remarkable in this category is the relatively high number of papers of cell enumeration and differentiation in other body fluids than blood [103, 109, 114–118].

Next to hematology analyzers, *CCLM* has published papers on coagulation analyzers, both for central laboratory and point-of-care use [119–124], analyzers for digital image analysis of blood cell smears [125–129] and recently also on automated analyzers for measuring erythrocyte sedimentation rate [130, 131]. The most singular paper in this category was probably the one devoted to a multicenter ektacytometer evaluation study [132]; few labs will consider this instrument for their key inventory, but the number of citations (about six per year) shows that this very analyzer attracted the interest of other researchers.

Reference intervals

Traditionally, *CCLM* is one of the few journals that provide ample space for papers on reference intervals of clinical laboratory measurements and the theoretical concepts behind it. Also the domain of laboratory hematology is well represented in this category, with 18 papers over the last 10 years. Whereas many papers still use CLSI (Clinical & Laboratory Standards Institute) and ISLH (International Society for Laboratory Hematology) recommended procedures for establishing reference intervals, there is growing interest in indirect methods using data mining of large datasets by mathematical techniques [72, 133–137]. Although indirect methods generally yield reliable data and have gained wide acceptance [138], some caveats need to be taken into account [139].

Standardization and harmonization

Papers on standardization and harmonization in laboratory hematology remain relatively scarce in comparison with clinical chemistry. Without any doubt this is due to the lack of international standards and reference materials.

Table 2: The 20 most cited *CCLM* papers in the domain of laboratory hematology 2012–2022 (www.scopus.com, retrieved 13-09-2022).

Author(s)	Title	Publication year-month	Citations, n	Average citations per year, n
Henry et al. [150]	Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis.	2020–07	896	413.5
Han et al. [59]	Prominent changes in blood coagulation of patients with SARS-CoV-2 infection	2020–07	676	312.0
Hoffmann [85]	Reticulated platelets: analytical aspects and clinical utility	2014–08	105	13.4
Lippi and Favaloro [51]	Recent guidelines and recommendations for laboratory assessment of the direct oral anticoagulants (DOACs): is there consensus?	2015–02	90	12.3
Lippi and Plebani [63]	Red blood cell distribution width (RDW) and human pathology. One size fits all.	2014–09	89	11.5
Lippi and Plebani [151]	EDTA-dependent pseudothrombocytopenia: further insights and recommendations for prevention of a clinically threatening artifact	2012–08	89	8.9
Eller et al. [56]	Dabigatran, rivaroxaban, apixaban, argatroban and fondaparinux and their effects on coagulation POC and platelet function tests	2014–06	86	10.8
Hu et al. [152]	Red blood cell distribution width is a potential prognostic index for liver disease	2013–07	72	8.0
Hoffmann et al. [70]	Effect of age and gender on reference intervals of red blood cell distribution width (RDW) and mean red cell volume (MCV)	2015–12	62	8.8
Stotz et al. [153]	The lymphocyte to monocyte ratio in peripheral blood represents a novel prognostic marker in patients with pancreatic cancer	2015–03	62	8.5
Franchini and Liumbruno [154]	ABO blood group: old dogma, new perspectives	2013–08	62	7.0
Halbmayer et al. [155]	Interference of the new oral anticoagulant dabigatran with frequently used coagulation tests	2012–09	60	6.2
Favaloro and Thachill [58]	Reporting of D-dimer data in COVID-19: some confusion and potential for misinformation	2020–08	59	30.0
Hoffmann et al. [156]	Discriminant indices for distinguishing thalassemia and iron deficiency in patients with microcytic anemia: a meta-analysis	2015–12	59	9.0
Bruegel et al. [107]	Comparison of five automated hematology analyzers in a university hospital setting: Abbott Cell-Dyn Sapphire, Beckman Coulter DxH 800, Siemens Advia 2120i, Sysmex XE-5000, and Sysmex XN-2000	2015–07	57	8.2
Fleming et al. [103]	Validation of the body fluid module on the new Sysmex XN-1000 for counting blood cells in cerebrospinal fluid and other body fluids	2012–10	55	5.6
Shi et al. [157]	Antiphosphatidylserine/prothrombin antibodies (aPS/PT) as potential diagnostic markers and risk predictors of venous thrombosis and obstetric complications in antiphospholipid syndrome	2018–04	52	12.0
Lippi et al. [158]	Red blood cell distribution width is significantly associated with aging and gender	2014–09	51	6.5
Magrini et al. [159]	Comparison between white blood cell count, procalcitonin and C-reactive protein as diagnostic and prognostic biomarkers of infection or sepsis in patients presenting to emergency department	2014–10	50	6.5
Zierk et al. [134]	Indirect determination of pediatric blood count reference intervals	2013–04	50	5.3

Yet, in the last decade *CCLM* published 14 papers in this category, almost double the percentage of prior years (Table 1). Coagulation assays clearly constitute the largest part [49, 140–145], whereas initiatives in hemocytometry standardization are lagging far behind [146–148]. The recommendations by the Italian Society of Clinical Chemistry for harmonization of interpretative comments added to hematology reports form a rare, but very welcome exception that hopefully will be followed in other countries [149].

Highly cited *CCLM* papers in laboratory hematology

Table 2 shows the top-20 highest cited *CCLM* papers in the domain of laboratory hematology published during the last decade. Two publications on Covid-19 and SARS-CoV-2 stand out with 300–400 citations per year since they were printed [59, 150]; the impact and the urgency of the pandemic are doubtlessly explaining the very high citation rate. To a lesser extent this was also the case for a third Covid-19 related paper [58]. All other papers in Table 2 reached an annual citation rate between 5 and 13 and they all belong to one of the categories mentioned above. In our opinion this indicates that recent advances in laboratory hematology published in *CCLM* are well perceived by other researchers.

Conclusions

Over the last decade, *CCLM* has seen a steady increase of laboratory hematology publications, both in absolute and relative sense. Almost 16% of all *CCLM* papers now belongs to the laboratory hematology discipline. In addition, these papers are generally well received by the scientific community as indicated by their citation rates. Also, laboratory hematology papers are very likely to have contributed to the very significant rise in impact factor that *CCLM* recently experienced [160]. Moreover, newer topics in the domain of the discipline are emerging and are very likely to form the subject of future papers in *CCLM*, for example in the field of RBC parameters, hemoglobinopathy, coagulation assays and drugs and WBC cell population data generated by hematology analyzers. Taken together, this proves that the journal represents a valuable medium for dissipating information on new developments in the laboratory hematology discipline.

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