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Automated detection of neutropenia using noninvasive video microscopy of superficial capillaries

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To the Editor:

Cancer patients undergoing cytotoxic chemotherapy are at elevated risk of developing serious infections[1]. The risk of developing these infections increases when white blood cell (WBC) counts, particularly the absolute neutrophil counts (ANC), are reduced. This reduction in neutrophil counts, the most abundant white-blood-cell subtype, is referred to as

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Authorship Contributions

APT collected and analyzed data, implemented critical elements of the software pipeline, and wrote substantial sections of the manuscript; IB analyzed data, provided substantial support in data interpretation, and provided substantial support in software development and quality control; MJLC supervised the development of the proposed pipeline and contributed in the analysis and interpretation of results; TV analyzed data, conceived the software-pipeline structure, and implemented critical elements of the software pipeline; ASF collected data, analyzed results, and provided substantial support on data interpretation; LS, NJD, and AMB provided technical advice and contributed in the manuscript revision; CC, KH, MFU, CDR, and BV made substantial contributions to patient recruitment and data acquisition; YBC and EPH made substantial contributions to the conception and design of our clinical study; CCG and AB made substantial contributions to the conception of the initial technological concept, the design of the clinical study, experimental framework, data acquisition, the analysis and interpretation of data, and supervised the manuscript writing and the overall development of the proposed method; All authors revised the article critically for important intellectual content and approved of its submission.

Disclosure of Conflict of Interest

All other authors have nothing to declare.

neutropenia, with these infection episodes termed febrile neutropenia (FN). Patients have a high risk of developing FN during sustained severe neutropenia[1] (ANC<500/μL), which is a common side effect of cytotoxic chemotherapies. FN occurs frequently, currently in approximately one in six of all chemotherapy patients[2], and it is associated with a high rate of mortality[3], where 11% of patients die after one or several hospitalizations[4,5]. In the US alone, the associated cost due to such hospitalizations accounts for $2.7B dollars annually[2], contributing to up to 40% of the total cost of cancer treatments[6].

Early detection of severe neutropenia can be key to preventing FN. Timely detection could enable preventive therapies, such as Granulocyte-Colony Stimulating Factors (GCSF)[7] or prophylactic antibiotics, to be administered. Unfortunately, current neutrophil monitoring options are inadequate to monitor severe neutropenia with sufficient frequency to allow for early detection and therapy optimization. Their reliance on the extraction and analysis of blood samples, which requires trained medical oversight, typically limits this testing to clinical settings. Cost-effective high frequency monitoring of this parameter, therefore, requires a new method that can be used by outpatients with minimal risk.

To address this unmet need, we propose the first noninvasive technology that can automatically screen patients for severe neutropenia without requiring blood draws, thus enabling patients to have more frequent access to this test. Our proposed noninvasive device is a compact microscopy system that can acquire high-resolution, high-frame-rate videos of superficial capillaries (Figure S1)[8], coupled with an automated software pipeline that can analyze those videos for a measurement of neutropenia. This design potentially opens the door to the use of such instrumentation in the patient's home. We conducted a clinical study at two independent hospitals to assess the ability of our device and algorithm to detect severe neutropenia in chemotherapy patients undergoing standard therapy. In previously reported work[8], we demonstrated an initial proof-of-concept of this principle using a small set of nailfold capillary video samples[8], which were manually analyzed through visual inspection by human experts. Here, we further demonstrated and validated a fully automated software analysis pipeline and extended our results to a larger cohort of 44 patients.

The individuals enrolled in our study were selected from patients undergoing high-dose chemotherapy followed by Autologous Stem Cell Transplantation (ASCT) at the Massachusetts General Hospital (MGH) Boston, MA, USA, or at Hospital Universitario La Paz (HULP), Madrid, Spain. This specific patient population was selected due to its clinical relevance and highly standardized regimen which allows for predictable evolution of neutrophil count dynamics, ensuring a transition from baseline values (ANC>500/μL) to severe neutropenia (ANC<500/μL), as well as an opportunity to acquire multiple video samples at different time points (Figure S2). The protocol was approved by the corresponding IRB boards for a total of 44 patients to be included in this study (Supplementary Methods).

From the 44 enrolled subjects, video sessions containing at least one suitable capillary in their field of view were collected (Supplementary Methods) at different stages of the ASCT treatment (Figure S2). Specifically, a technical operator ensured that at least one capillary fulfilled the required quality criteria for analysis[8]. This resulted in a total of 115 imaging

sessions from 42 subjects, with an average of three sessions per subject. Each imaging session is associated with a reference blood test performed by the gold-standard clinical-laboratory analyzer whose values, including the reference ANCs, are provided in the Supplementary Methods (Figure S3). To confirm the findings of our previous work correlating the number of capillaries analyzed with the classification accuracy[8], we evaluated the diagnostic performance of our automatic pipeline on three distinct sets of imaging sessions: those that had at least one suitable capillary (all 115 imaging sessions from all 42 patients), at least two (100 sessions from 38 patients), or at least three (89 sessions from 35 patients).

Following the acquisition of these sessions using our clinical prototype[8], an automated software pipeline composed of several processing steps (Supplementary Methods) was designed to analyze the raw videos. The analysis of each video session produced a separate data point consisting in a unitless “Leuko Index”, which was used to classify severe-neutropenic cases (ANC<500/μL) from the rest (ANC>500/μL). To produce this index, our pipeline first detected nailfold capillaries in the corresponding video session, then counted passing optical-absorption gaps —which as discussed in Bourquard et al 2018[8] can be considered as proxies of flowing neutrophils — inside these capillaries, and finally averaged the individual capillary counts into one single value. Results were then compared against the gold-standard ANC values to determine performance in separating severely neutropenic patients (ANC<500/μL) from the rest (ANC>500/μL), giving the opportunity to calculate the rate of correctly-classified severe neutropenia cases (true positives) against the rate of false alarms (false positives).

The classification performance for all imaging sessions, with at least three suitable capillaries detected, yielded an Area Under the Curve (AUC)[9] of 0.95 (Figure 1). The use of all imaging sessions with at least one suitable capillary yielded an AUC of 0.91 (Figure S4), whereas those containing at least two suitable capillaries yielded an AUC of 0.94 (Figure S5). The intra-measurement agreement of our method when using only one, two or three capillaries per imaging session was shown to increase as more capillaries were used (87% agreement when using 1 vs. 2 capillaries and 91.4% agreement when using 2 vs. 3 capillaries), see Figure S6. Also, the classification performance improved with the amount of analyzed capillaries per session, with the percentage agreement increasing from 69.8% to 90.9% (Figure S6), which also corroborates previous results[8].

These results demonstrate, for the first time, that our noninvasive optical system (Figure S1), coupled with the proposed automated video analysis pipeline (Figure S7), is able to detect severe neutropenia with high accuracy in a patient cohort showing various degrees of ANC values (Figure S3), without the need for a blood draw. Future work includes the refinement of the device hardware to increase the number of suitable capillaries detected in a single session. The current analysis methods may also be adapted in the future to perform quantitative ANC measurements or differential detections of WBC subtypes.

Overall, this work demonstrates that patients can be screened for severe neutropenia automatically and noninvasively without the need to draw blood. Our noninvasive blood

analysis method opens the door to frequent, precise and personalized management of patients at risk for febrile neutropenia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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CCG, IB, AB, and ASF have an issued patent on the proposed technology under patent number US 9,984,277 B2 and title “Systems, Apparatus, and Methods for Analyzing Blood Cell Dynamics”. APT, IB, ASF, AB, and CCG report honoraria, financial support from, and current employment by Leuko Labs Inc. to conduct this research. IB, ASF, CCG, and AB hold equity in Leuko Labs Inc.

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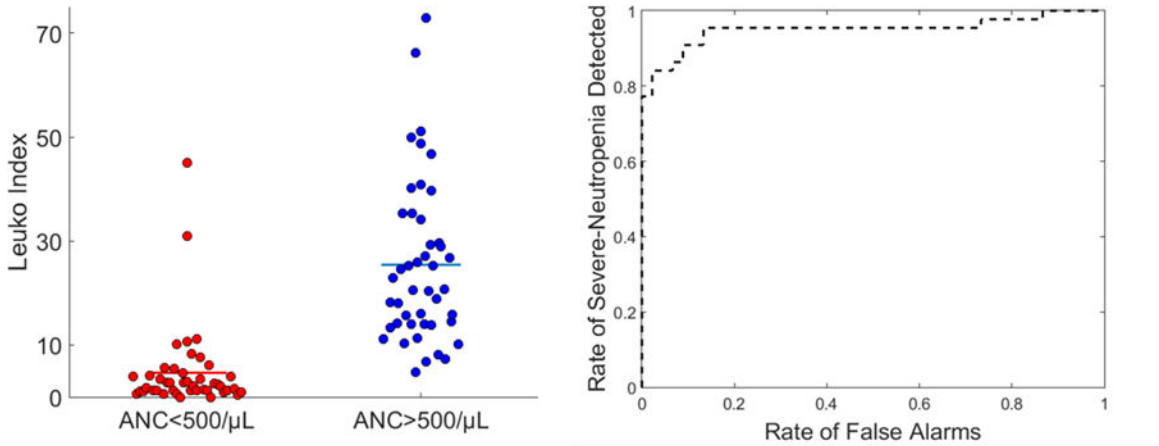

Figure 1.

(Left) noninvasive imaging sessions (red and blue markers), acquired from chemotherapy patients in our study, were automatically analyzed by our software pipeline to yield a "$\text{Leuko}_{\text{index}}$" result which can be used to perform a classification with respect to the corresponding gold-standard ANC values obtained from blood tests. Each classification result is associated either with a severe-neutropenic reference state (ANC<500; red markers) or above (ANC>500; blue markers). Results corresponding to imaging sessions containing at least three suitable capillaries are shown. (Right) Receiver Operating Characteristic (ROC) curve associated with this classification (AUC = 0.95, 35 patients, and N =89 imaging sessions).