Towards Quantitative Assessment of Calciphylaxis

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ABSTRACT

Calciphylaxis is a rare disease that has devastating conditions associated with high morbidity and mortality. Calciphylaxis is characterized by systemic medial calcification of the arteries yielding necrotic skin ulcerations. In this paper, we aim at supporting the installation of multi-center registries for calciphylaxis, which includes a photographic documentation of skin necrosis. However, photographs acquired in different centers under different conditions using different equipment and photographers cannot be compared quantitatively. For normalization, we use a simple color pad that is placed into the field of view, segmented from the image, and its color fields are analyzed. In total, 24 colors are printed on that scale. A least-squares approach is used to determine the affine color transform. Furthermore, the card allows scale normalization. We provide a case study for qualitative assessment. In addition, the method is evaluated quantitatively using 10 images of two sets of different captures of the same necrosis. The variability of quantitative measurements based on free hand photography is assessed regarding geometric and color distortions before and after our simple calibration procedure. Using automated image processing, the standard deviation of measurements is significantly reduced. The coefficients of variations yield 5-20% and 2-10% for geometry and color, respectively. Hence, quantitative assessment of calciphylaxis becomes practicable and will impact a better understanding of this rare but fatal disease.

Keywords: Calciphylaxis, Photography, Skin necrosis, Geometric registration, Color calibration, Quantitative measurements, Wound management, Scale invariant feature transform (SIFT)

1. INTRODUCTION

Calciphylaxis (calcific uremic arteriolopathy, CUA) is still an incompletely understood rare disease, which most often affects patients on haemodialysis [1]. It has devastating conditions associated with high morbidity and mortality. CUA is characterized by systemic medial calcification of the arteries, but unlike other forms of vascular calcifications, CUA affects small vessel by mural calcification with or without endovascular fibrosis or thrombosis yielding painful, ischemic, partly necrotic skin ulcerations. Pathomorphologically, media calcification of cutaneous arterioles and extracellular matrix remodeling are the hallmarks of the disease.

So far, quantitative wound measurement is not performed in clinical routine. The gold standard for measuring wounds is planimetry, i.e. tracing the perimeter of the wound on transparent acetate with a fine-tip marker, then calculating the surface area by counting grids manually or with a digitizing pad [2,3]. Planimetry, however, is strongly affected by the image source, which usually is neither calibrated nor standardized. Yi et al. have suggested special hardware for standardized 3D imaging of wounds, which limits the applicability of this kind of measurements [4]. Still, a simple but reliable method has not yet been proposed towards quantitative assessment of skin lesions.

In this paper, we aim at supporting the installation of multi-center registries for rare calciphylaxis disease including a photographic documentation of skin necrosis. In particular, the variability of quantitative measurements based on free hand photography is assessed regarding geometric and color distortions before and after a simple calibration procedure.

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2. MATERIAL AND METHODS

In this section, we will address the application domain of normalizing un-calibrated free-hand photography, the solution based on standard components of medical image processing, and the evaluation of our method.

2.1 CUA Registry

Due to the rareness of the CUA disease, a multi-center registry has been developed where standardized patient records are collected [5,6]. The electronic case report forms (eCRF) include photographic documentation of skin necrosis. So far, there is no control of imaging device, illumination, lenses and scale, but a simple ruler is used for reference (Fig. 1). Such uncontrolled conditions will not be avoidable in future, since images will be captured always in different locations, by different personnel using different hardware, and the illumination of necrosis is particularly dependent on the patient's room.

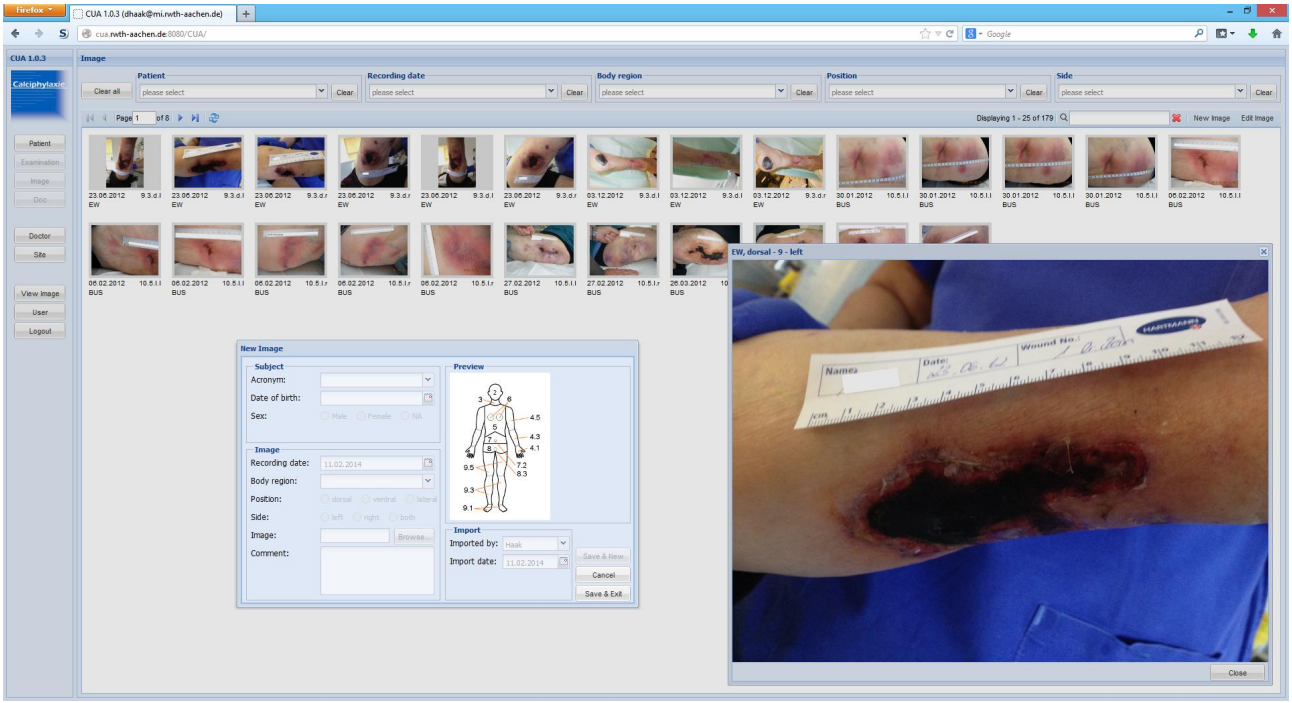

Figure 1: Screenshot of the German CUA Registry with an overview of photographic necrosis documentation.

On the other hand, size and color of the necrotic lesion are particularly important for clinical assessment of the disease and evaluation of the CUA therapy. If not measured absolutely, at least a quantitative assessment of its relative changes, normalized to the specific subject, is desired and will provide further impact to medical care and outcome.

However, the only reliable method of increasing standardization in imaging is a written standard operation procedure (SOP), which is handed to the study nurses capturing the images and entering the data into the electronic registry. Such SOPs are well known means in controlled clinical trials as well as clinical registries, and study nurses are familiar with it and usually compliant [7,8]. The CUA SOP is describing (i) how in general the patient and her room are prepared optimally (e.g., avoiding occlusions of the lesion, avoiding any artificial bending of the skin, allowing as much light as possible to illuminate the important art of the skin), (ii) how the reference object is optimal positioned (i.e., in plane with the lesion, close to the lesion but not covering it), and (iii) how a digital camera is initialized obtaining most sharpness (e.g., direction and distance to the lesion, capturing cylindrical surfaces, avoiding distortions).

2.2 Image Acquisition

Despite such SOPs, in particular if photographs are taken using different consumer devices, color and brightness as well as geometry may vary considerable and distortions from lenses and aperture may further affect the images. In order of standardizing, a consumer color reference card is used (Fig. 2). This card yields geometric and color references, since the colors of the plates and the size of the card is reproducibly controlled. In addition, a ruler has been placed in the image as it has been used before. In compliance with the written SOP, the proposed setting yields most value of images for further quantitative analysis.

Figure 2: Reference card (2 x 3 inches, 24 color plates, CameraTrax, USA).

2.3 Image Processing

Image processing is designed to be performed without any user interaction. Hence, all algorithms in use must be capable to handle the large variety of images in appearance, pixel resolution, and other properties. Therefore, only simple and robust methods are used to design the three-step procedure: (i) localization of reference object, (ii) color normalization, and (iii) geometric and scale normalization.

2.3.1 Localization of reference card

Derived from linear system theory – as optical imaging is conforming to – matched filters are the optimal detectors for localization of known objects in noisy images. However, a matched filter is inappropriate if the size and/or orientation of the object is changed. In 1999, Lowe has established a robust method of object detection using the scale invariant feature transform (SIFT). Using SIFT, keypoints are extracted at image locations of high contrast. Each keypoint is characterized by a feature vector obtained from a local multi-scale analysis [9]. The feature vectors can be used to align keypoints from different images (Fig. 3).

Figure 3: SIFT keypoint correspondences as found between the card imaged for reference and placed beside the patient.

The procedure is illustrated in Figure 3. The photographic documentation of a lesion (Fig. 3, right hand side) shows all, the lesion, the color card reference and the ruler. In such images, keypoints are detected anywhere. Likewise, the algorithm extracts many keypoints in an image of the reference card, as shown in Figure 2. Deriving correspondences

between the images based on the features describing the keypoint, most candidate points in either the input images are dismissed, and only a few valid point pairs are remaining. For example in Figure 3, a total of 13 points have survived the comparison process. Except point No. 13, all correspondences are correct.

2.3.2 Extraction of reference card

In an image plane, each picture element (pixel) is described by a tuple (x,y). The cards as shown in Figure 3a and 3b geometrically differ by a perspective transform, which is described completely by a set of by 8 parameters $a_1 \ldots a_8$:

$$x' = \frac{a_1\, x + a_2\, y + a_3}{a_7\, x + a_8\, y + 1}\ , \qquad y' = \frac{a_4\, x + a_5\, y + a_6}{a_7\, x + a_8\, y + 1}$$

Here, (x,y) and (x',y') determine the pixel coordinates in the image planes before and after the perspective transform, respectively. Using holomorphic coordinates, a least-squares approximation is applied to determine the best fitting transform of the keypoints from the template to the photograph. The least-squares process provides sufficient robustness to cope with outliers, as, for instance, point No. 13 in Figure 3.

2.3.3 Color calibration

Color calibration of each image starts with the measurement of the 24 colors on the color reference card depicted in the image. In red, green, blue (RGB) color space, each color is represented by a triple (r,g,b) and (r',g',b') in source and target image, respectively. These triples are averaged from the entire color field, again increasing robustness. Assuming an affine three-dimensional transform in RGB color space, a set of 12 parameters $c_1 \ldots c_{12}$ must be determined:

$$r' = c_1\, r + c_2\, g + c_3 b + c_4\ , \qquad g' = c_5\, r + c_6\, g + c_7 b + c_8\ , \qquad b' = c_9\, r + c_{10}\, g + c_{12} b + c_{12}$$

Again, this is robustly done using a least-squares approximation based on the 24 measured pairs of color triples, where the reference RGB values are set according to the color card documentation. For color normalization, the computed color transformation is applied to all pixels of the image, resulting in the final color calibrated image.

2.3.4 Scale calibration

Geometric adjustment may also be based on the reference color card. Since the absolute dimensions of the card are known, all photographs, disregarding the number of pixels in the sensor, the lenses and other parameters affecting the scale of objects, are transformed such that the resulting image yields the same number of pixels in x and y dimensions of the color card. Assuming the card is placed on top of the region of interest (ROI), this would result in an absolute normalization. It is, however, only possible to place the card beside the lesion (ROI), and geometric adjustment turns into an approximation. The SOP as mentioned in Section 2.1 is used to have this approximation as good as possible.

Alternatively, the ruler may be used to normalize the scale. Here, the distance between two points on the ruler is mapped onto a fixed distance in pixel. Normalization is computed by symmetrically scaling along the x and y axes using cubic interpolation, such that the length of the ruler becomes the same in each of the images. Again, this approach is applicable only if the ruler is aligned in the plane of the skin lesion, which is tried to be ensured by the imaging SOP.

2.4 Evaluation Study

In a first evaluation study, we multiply capture a skin lesion using different camera, lenses, and flash lights. Between imaging, the patient was re-positioned. In total, 10 photographs have been acquired from two different body parts of a subject. In each image, three regions were marked for color and size measurement (Fig. 4). Mean and standard deviations were recorded.

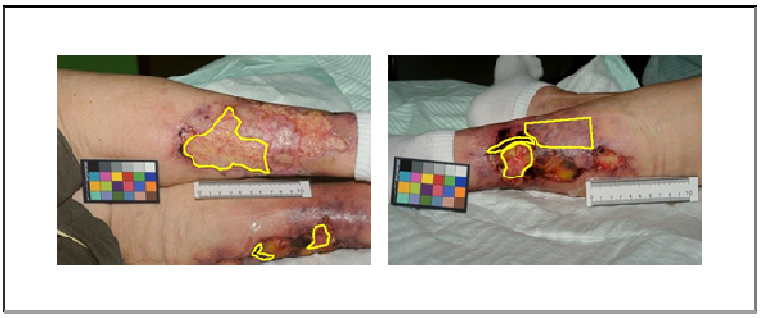

Figure 4: Areas marked for quantitative assessment of lesion's color and size for left leg (areas 1 to 3) and right leg (areas 4 to 6) leg.

In probability theory and statistics, the coefficient of variation C_v is a normalized measure of dispersion of a probability distribution. It is also known as unitized effective risk, variation coefficient, or relative standard deviation (RSD) and computed as the ratio of the standard deviation σ to the mean μ:

$$C_v = \frac{\sigma}{\mu}$$

In our study, the coefficient of variation is computed to indicate robustness of color and size measurements before and after according calibrations. Reliable measures shall have a C_v below 5%, and the C_v is expected to decrease if the normalization procedure is effective.

2.5 Case Study

In addition, the proposed technique was applied to a subject that has been imaged subsequently in follow up of the disease's development. Different imaging hardware has been used to collect the image data by several study nurses. On a total of 8 images, the quality improvement due to our normalization procedure is evaluated qualitatively.

3. RESULTS

3.1 Evaluation Study

Figure 5 shows some of the images that have been acquired in different poses, illumination and perspective (upper row). The normalization obtained with the proposed procedures is depicted I the lower row. As it is clearly seen, both the color and the size of lesion are unified.

Table 1 shows the quantitative results obtained from the evaluation study. Due to the different resolutions of the camera systems used for image acquisition, the sizes were measured in percent of the entire image or all areas considered. More important, the standard deviation was decreased significantly for all areas, which is indicating meaningful geometric registration and size adjustment. The same results in principle hold for the mean color measured within the areas. Standard deviations of measures are reduced significantly due to the proposed image calibration and normalization scheme.

Regarding the C_v values, un-calibrated size assessment has variations of up to 50%, which is reduced by calibration to 5% up to 20%. For color measures, the C_v was reduced to 2% up to 10%. Although this is still too large to be considered reliable, it may support relative assessment where, for instance, different parts of the skin lesion are measured without an absolute scale.

3.2 Case Study

Figure 6 depicts the results of the case study. After normalization of size and color (Fig. 6, lower row), the colors of surrounding skin are appear more similar than in the original images. Also, the size of the reference card is unified.

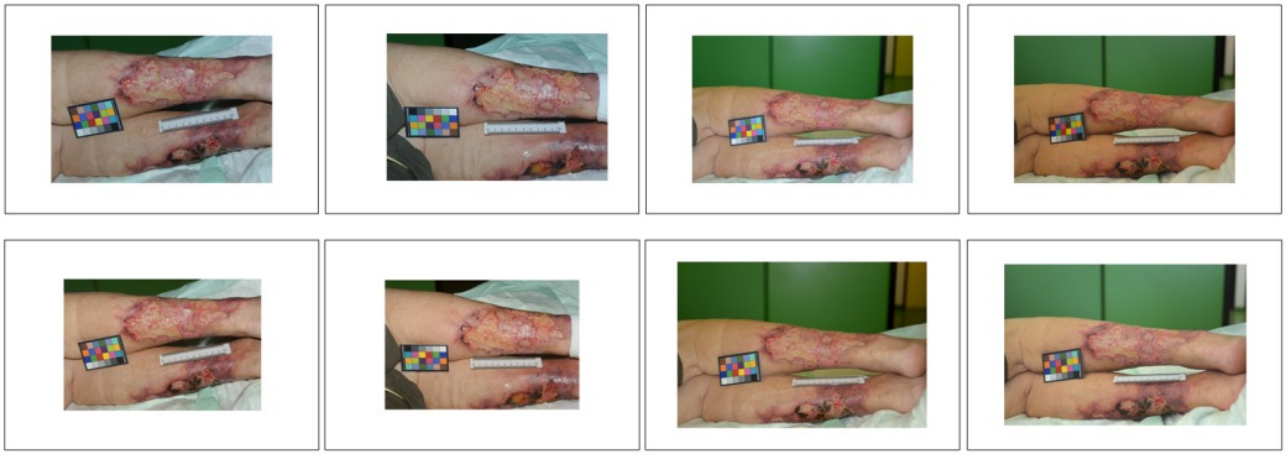

Figure 5: Photographic documentation of CUA using a color card and a ruler for calibration. Upper row: four images in different poses, illumination, and photographic perspective. Lower row: calibration regarding both geometry and color.

Lesion label	Geometry Un-calibrated Mean size in %	Std Dev in %	Geometry Calibrated Mean size in %	Std Dev in %
Area 1	0.632	0.316	0.474	0.071
Area 2	1.683	0.826	1.255	0.150
Area 3	0.298	0.132	0.235	0.053
Area 4	0.575	0.075	0.303	0.075
Area 5	3.210	0.860	1.586	0.071
Area 6	0.161	0.025	0.082	0.006
Lesion label	Color Un-calibrated Mean (R/G/B)	Std Dev	Color Calibrated Mean RGB	Std Dev
Area 1	(151.0/87.0/68.2)	(26.7/20.0/24.6)	(162.6/95.6/79.0)	(3.2/8.8/14.8)
Area 2	(152.4/98.0/88.4)	(16.8/20.9/28.7)	(163.4/107.4/101.2)	(8.7/8.7/11.2)
Area 3	(60.8/47.0/40.2)	(13.5/7.2/9.2)	(64.8/51.6/45.0)	(9.5/19.0/22.9)
Area 4	(129.6/76.2/63.8)	(17.2/15.6/19.2)	(145.2/86.2/72.2)	(5.1/8.8/9.2)
Area 5	(172.8/124.0/101.0)	(10.9/11.7/17.3)	(191.2/137.4/112.6)	(3.6/3.2/5.1)
Area 6	(44.8/37.2/33.8)	(12.0/9.8/10.5)	(55.4/42.4/36.0)	(10.3/7.5/8.3)

Table 1: Results of the evaluation study. The areas of measurement are indicated in Figure 4.

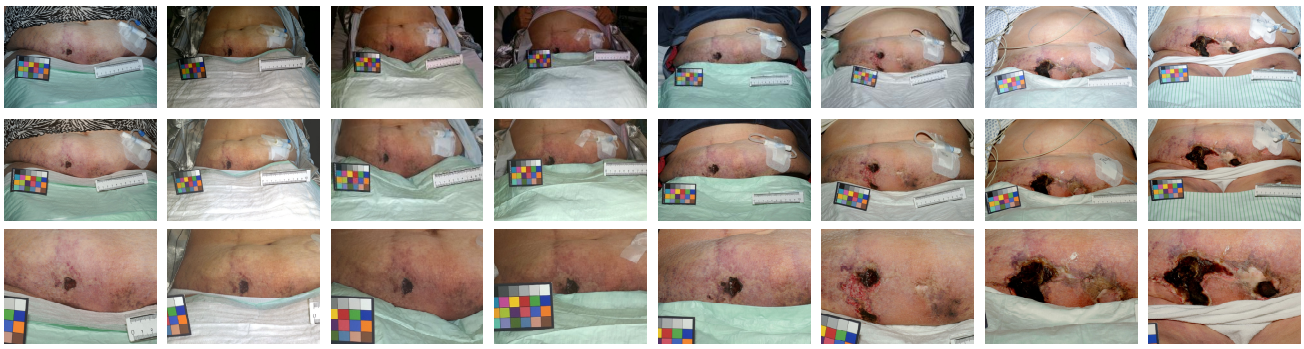

Figure 6: Images of the case study before (upper row) and after (middle) calibration with acquisition dates indicated. The lower row show the lesion ROI extracted from the images.

4. DISCUSSION

Calciphylaxis is a rare disease that has devastating conditions associated with high morbidity and mortality. Using a simple color chart or ruler calibration device, which is placed into the picture according to a written SOP, skin lesions such as necrotic ulcerations become quantitative assessable using photographic consumer equipment and automated image processing. We have shown that calibration in geometry and color is possible for different imaging devices, and significantly reduces the standard deviations of quantitative measurements. Based on this result, the CUA registry will collect photography of wounds, and using the quantitative color measures, a classification scheme can be developed that works on images from all camera systems, including smart phones.

Molnar et al. have already suggested the use of standardized quantitative photography in a multi-center web-based study [10]. However, their photographs have been acquired in all centers using the same hardware and camera. This yields in a better standardization as we can obtain for a multi-center registry for rare diseases. Furthermore, scale and color normalization was performed manually. More recently, Shetty et al. have suggested a novel technique of photographic wound assessment, where a printed grid is placed in the image and an ImageJ program was used for geometric alignment [11]. The authors were showing that this type of processing is superior to common ruler-based measurements.

Accordingly, our card provides a similar grid, but also supports color normalization. In contrast to Shetty et al. [11], we compute a perspective projection model based on automatic detected keypoints, while Shetty et al. simply project a rectangle over their card to measure its size. In contrast to Molnar et al. [10], we aim at fully automatic processing of non-standardized photography, which – to the best of our knowledge – has not jet been suggested in the scientific literature.

5. CONCLUSION

In conclusion, a simple color chart and length normal allow for automated calibration of wound photography. For rare diseases such as the CUA, multi-center registries can be established including photographic documentation of wounds. In multi-center trials, standardization of optical imaging modalities is almost impossible due to different cameras, light conditions, and study nurses during the photography. However, our approach reduces variance in quantitative measures of size and color.

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