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ORIGINAL RESEARCH

Validity of First-Time Diagnoses of Darier's Disease in the Danish National Patient Registry

Inger LH Dorf[1]
Sigrún AJ Schmidt[1,2]
Mette Sommerlund[1]
Uffe Koppelhus[1]

[1]Department of Dermatology, Aarhus University Hospital, Aarhus, Central Region Denmark, Denmark; [2]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Central Region Denmark, Denmark

Purpose: Darier's disease (DD) is a rare genetic skin disease, characterized by yellow-brown, scaly, crusted papules in seborrheic areas and specific nail changes. This study aimed to validate all first-time diagnoses of DD in Danish National Patient Registry (DNPR). The intent of the study is validation of DNPR for epidemiological and clinical studies on DD.

Patients and Methods: We identified all patients in DNPR who received their first-time diagnosis of DD between January 1, 1977 and December 31, 2018 (International Classification of Diseases [ICD]-8 code 75721 until the end of 1993: ICD-10 code Q828F thereafter). We restricted to diagnoses from departments of dermatology, where these patients are managed. We validated diagnoses against information from medical records, using predefined data extraction sheets and validation criteria. We classified diagnoses as probable when characteristic clinical features were present; confirmed when there was also genetic confirmation, histopathological confirmation and/or positive family history, or rejected (remaining patients). We estimated positive predictive values (PPVs) with 95% confidence intervals (CIs) for diagnoses overall and stratified by ICD classification, sex, age at diagnosis, year of diagnosis, type of diagnosis, and type of contact.

Results: We identified 277 first-time diagnoses of DD, of which 229 (82.7%) stemmed from departments of dermatology. Medical records were available for 196 (85.6%) of these. The overall PPVs for probable and confirmed DD were 89.3% (95% CI: 84.2–92.9) and 81.1% (95% CI: 75.1–86.0), respectively. The PPV for probable ICD-8 diagnosis (95.8% (95% CI: 82.1–99.5)) was slightly higher than that of probable ICD-10 diagnosis (88.4% (95% CI: 82.7–92.3)).

Conclusion: The validity of first-time diagnoses of DD recorded by departments of dermatology in the DNPR is relatively high, making DNPR suitable for epidemiological studies on DD in Denmark, as well as a useful source for recruitment to clinical studies on DD.

Keywords: Denmark, diagnosis, dyskeratosis follicularis, health administrative data, registration, validity

Introduction

Darier's disease, also known as dyskeratosis follicularis, is a rare genetic skin disease (genodermatosis) caused by variants in the gene *ATP2A2*, which encodes the Ca^{2+}-ATPase, SERCA2, in the endoplasmic reticulum.[1] To this date, more than 240 disease-causing variants, primarily missense and frameshift, have been identified.[2] The mode of inheritance is autosomal dominant with complete penetrance but variable expressivity. With only few exceptions, clear genotype-phenotype correlations linking specific disease manifestations and variants have yet to be established.[1,2]

Correspondence: Inger LH Dorf
Department of Dermatology, Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, Aarhus, 8200, Denmark
Tel +45 7846 1861
Email inger.dorf@live.dk

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Based on a very limited number of studies, the prevalence of Darier's disease is estimated to be between 1:100.000 and 1:36.000,[2,3] with an equal sex distribution.[4] Darier's disease presents typically in adolescence, most commonly at the onset of puberty.[2] The clinical features usually include yellow-brown, scaly or crusted papules in seborrheic areas on the scalp, face, truncus and sides of the neck.[3,4] Other characteristic traits are seen with varying expressivity, such as flat, wart-like papules on the dorsal side of hands and feet, palmo-plantar hyperkeratinized papules, papular lesions in the axillas and groins, whitish papules in the oral mucosa, and various nail changes (longitudinal lines and fissures, subungual hyperkeratoses, brittleness, and distal V-shaped notches).[1,2,5] Histopathological examination of affected skin in Darier's disease reveals acantholysis and dyskeratotic cells called "grains" and "corps ronds".[2]

In Denmark, there is a long tradition for routine collection of data during health-care delivery, forming the basis for numerous nationwide registries.[6] One such registry is the Danish National Patient Registry (DNPR), which records details on patient contacts to all hospitals in Denmark. National registries as DNPR are the basis for many epidemiology studies on, eg, prevalence and comorbidity. While the positive predictive value of a common diagnosis such as acute exacerbation of chronic obstructive pulmonary disease (COPD) may be quite high,[7] we need to access the validity of rare diseases such as Darier's disease.

Two previous studies from our research group at the Department of Dermatology at Aarhus University Hospital evaluated the validity of the diagnoses of congenital epidermolysis bullosa and inherited ichthyosis in the DNPR.[8,9] The positive predictive values (PPVs) for diagnoses of epidermolysis bullosa ranged from 30.8% to 76.7%, while the ichthyosis diagnoses had PPVs just below 75%.[8,9] This study is, to our knowledge, the first to validate the diagnosis of Darier's disease in a National Patient Registry. In the present study, we therefore aimed to validate all first-time diagnoses of Darier's disease recorded by Danish hospital dermatology departments in the DNPR between 1977 and 2018.

Materials and Methods

Setting and Data Sources

The Danish health-care system provides tax-financed medical treatment for all residents in Denmark.[6] The Danish Civil Registration System was introduced in 1968, and since then every resident in Denmark acquires a unique personal identifier (the central personal registration number) and a National Health Service Medical Card, which serves as identification in the health system and consequentially in the nationwide registries.[10]

The DNPR is a hospital registry that collects data on admissions to Danish hospital wards since 1977 and outpatient specialty clinics (ambulatory) and emergency room contacts since 1995. At the end of each patient contact, the treating physician is responsible of coding one primary diagnosis (the main reason for contact) and optional secondary (contributory) diagnoses, in accordance with the International Classification of Diseases (ICD).[11] The 8th revision of ICD (ICD-8) was used until 1994, when it was replaced by the 10th revision (ICD-10).[11] In addition to diagnoses, selected administrative data (eg, dates of admission and discharge) are recorded.[11]

Study Population

We identified all patients in DNPR who received a first-time diagnosis of Darier's disease between January 1, 1977 and December 31, 2018 (ICD-8 code 75721; Danish ICD-10 code Q828F).[12] For validation, we included patients who had their first-ever diagnosis recorded at one of the five Danish departments of dermatology. From 1977 to 1993 patients were diagnosed with an ICD-8 diagnosis (code 75721) and from 1994 to 2018 patients were diagnosed with an ICD-10 diagnosis (code Q828F). Besides diagnosis code and central personal registration number, the data extraction from DNPR included administrative information with the date of hospital contact, type of contact (outpatient or admitted patient) and type of diagnosis (primary or secondary).

Validation

At first, the first author reviewed all available medical records in the study population and extracted relevant information using the Research Electronic Data Capture (REDCap) tool. REDCap is a secure web application for building and managing online surveys and databases.[13] The data extraction sheet is shown in Supplementary Table 1. Afterwards, the registry diagnoses were validated against the extracted data using predefined criteria (Table 1). Validation was defined with two levels of certainty as either "probable" or "confirmed", If the extracted data did not fulfill the criteria for either of these categories, the diagnosis was (categorized as) rejected. As can be seen

Table 1 Validation Criteria for a Probable, Confirmed and Rejected Diagnosis of Darier's Disease

	Probable	Confirmed	Rejected
Criteria	• At least 2 of the following: • Characteristic Darier's disease skin lesions: yellow-brown, scaly, and crusted papules • Characteristic anatomical site of lesions: Seborrheic areas including the scalp, truncus, face, hair line and flexures • Characteristic Darier's disease nail changes: Longitudinal lines, fissures, subungual hyperkeratosis, brittleness, and V-shaped notches distally	• 2 or more probability criteria + 1 or more of the following: • Molecular genetic confirmation: identification of a relevant pathogenic variant in the ATP2A2 gene • Histopathological confirmation: characteristic histological findings in Darier's disease including acantholysis and dyskeratosis • Family history of Darier's disease: one or more family members with similar symptoms or confirmed diagnosis	• Failure to meet criteria for a probable diagnosis

from Table 1, we considered a registry diagnosis of Darier's disease's to be "probable" when at least two of three of the following clinical findings were described: 1) characteristic skin lesions Darier's disease (yellow-brown, scaly, crusted papules), 2) characteristic anatomical site of skin lesions (seborrheic areas: scalp, truncus, face, hair line and flexures), and 3) distinctive nail changes (longitudinal lines, fissures, subungual hyperkeratosis, brittleness, and V-shaped notches distally). The diagnosis of Darier's disease was considered "confirmed" when at least one of the following additional requirements were met: 1) molecular genetic confirmation (identification of a pathogenic variant in the *ATP2A2* as determined by the clinical geneticists), 2) histopathological confirmation (biopsy showing Darier's disease acantholysis and dyskeratosis), or 3) family history of Darier's disease (medical history with one or more family members with similar symptoms or a confirmed diagnosis). If the primary investigator (the first author) had any doubt during the review or validation process for a specific patient, UK or MS (co-authors with broad clinical experience in genodermatosis) were consulted.

Statistical Analysis

As an estimate of the validity of first-time diagnoses of Darier's disease, we calculated the PPV, that is, the proportion of patients with a validated diagnosis. We estimated the PPVs for both probable and confirmed diagnosis overall and stratified by ICD classification (ICD-8 or ICD-10), sex (male or female), age at diagnosis (<16 years, 16–30 years, 31–45 years, 45–60 years, or >60 years), year of diagnosis (before 2001, 2001–2008, or 2009–2018), type of diagnosis (primary or secondary), and type of contact (outpatient or admitted patient). We calculated 95% Confidence intervals (CI) using Wilson's method when the numerator was 40 or more, or else we used Jeffreys method.[14]

We registered clinical and administrative data from the records in REDcap, hosted at Aarhus University.[13] We performed statistical analyses in Stata (version 16.1, StataCorp LP, College Station, TX, USA).

Approvals

This study has been approved by the Danish Data Protection Agency (case number 1-16-02-668-15), by the Danish Patient Safety Authority (case number 3-3013-2483/1) and by the Division of Research Services (case number FSEID-00004307).

Results

Study Population

The study flowchart is shown in Figure 1. We identified 277 patients with a first-time diagnosis of Darier's disease recorded in the DNPR between 1977 and 2018: 229 patients (82.7%) from dermatological departments and 48 patients (17.3%) from other departments. Medical records were unavailable for 33 of the 229 patients (14.4%) diagnosed at departments of dermatology, leaving 196 patients (85.6%) for validation. The population eligible for validation had a slightly lower median age and proportion of males than the total population registered with a first-time diagnosis of Darier's disease, while the median age for the missing records were markedly higher than both of these groups (Table 2). In the total population, the ICD-8 diagnoses constituted 26% of the diagnoses, while this percentage was markedly lower in the validated population (only 12%) and

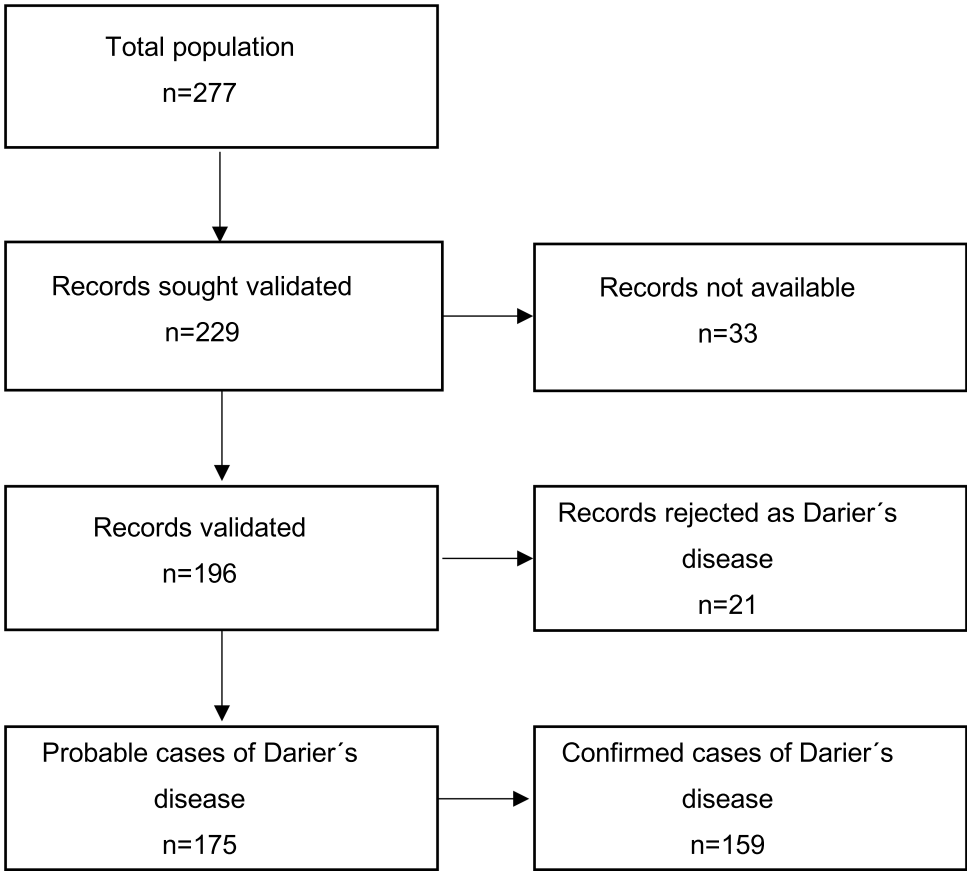

Figure 1 Flowchart illustrating the validation process.

significantly higher in the missing records population (73%). This difference was due to a disproportional number of missing medical records from early calendar periods (when ICD-8 was used), as the minimum required period for archiving had passed for many by the time of our review.

Table 2 Characteristics of Patients with a First-Time Diagnosis of Darier's Disease in the DNPR from 1977 to 2018

Characteristics	Total Population	Validated Population	Missing Records
Total, n (% of total)	**277 (100%)**	**196 (70.8%)**	**33 (11.9%)**
Female, n (% of total)	159 (57.4%)	119 (60.71%)	18 (54.6%)
Median age at diagnosis (IQR), years	39 (25–52)	35 (23–46)	52 (40–62)
Coding system for diagnosis			
ICD-8, n (% of total)	72 (26.0%)	24 (12.2%)	24 (72.7%)
ICD-10, n (% of total)	205 (74.0%)	172 (87.8%)	9 (27.3%)

Abbreviations: DNPR, Danish National Patient Registry; ICD, International Classification of Diseases.

Validation

Of the 196 first-time diagnoses evaluated, we classified 175 as probable Darier's disease, yielding an overall PPV of 89.3% (95% CI: 84.2–92.9) (Figure 2). Fourteen (66.7%) of the 21 rejected cases represented other dermatological diagnoses, including four cases each of Hailey-Hailey disease and Grover disease, and one case each of dyskeratosis congenita, bullous pemphigoid, pityrosporum folliculitis, actinic keratosis, warty dyskeratoma, and hereditary benign intraepithelial dyskeratosis. Six of the remaining rejected diagnoses had medical records suggestive of Darier's disease but did not meet the validation criteria. The true diagnosis of the last patient could not be classified based information in the medical record.

In the second-level validation, 159 patients (90.9% of probable cases) met the validation criteria for a confirmed diagnosis of Darier's disease resulting in a PPV of 81.1% (95% CI: 75.1–86.0). Of these, 32 (20.1%) had

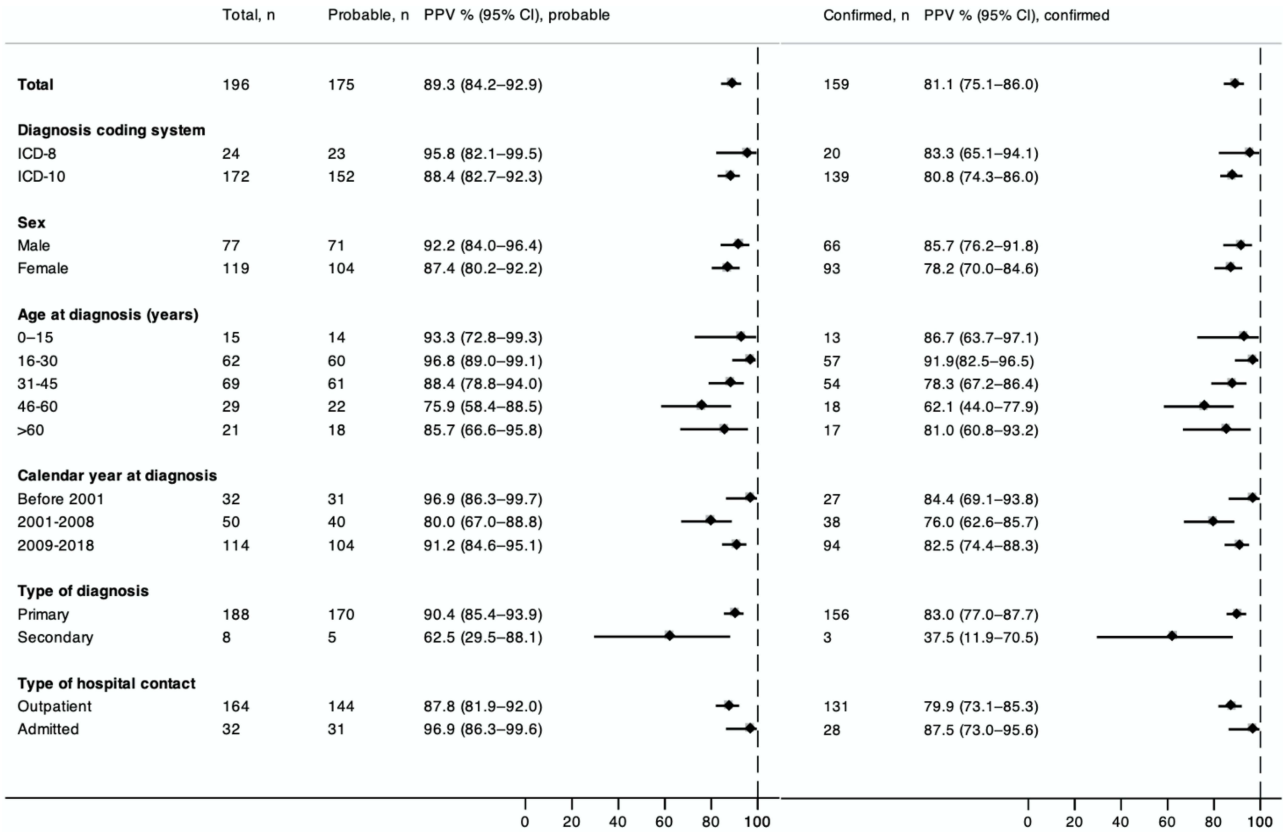

Figure 2 Positive predictive values for probable and confirmed first-time diagnosis of Darier's disease in the DNPR from 1977 to 2018, stratified by patient and diagnosis characteristics.

a confirmatory molecular genetic analysis, 119 (74.8%) had a confirmatory histological analysis and 99 (62.3%) had a positive family history of Darier's disease.

We observed PPVs of above 80% for both probable and confirmed ICD-8 and ICD-10 diagnoses of Darier's disease (Figure 2). We observed minor variation in PPVs in subgroups of sex, age at diagnosis, calendar year at diagnosis, and type of hospital contact (Figure 2). PPVs for probable diagnoses were above 75% for all subgroups, decreasing only slightly when considering confirmed diagnoses. Darier's disease recorded as a secondary diagnosis was uncommon (8 patients; 4.1%) and had low validity with PPVs for probable and confirmed diagnoses of 62.5 (95% CI: 29.5–88.1) and 37.5% (95% CI: 11.9–79.5), respectively. In comparison, the corresponding PPVs for primary diagnoses of Darier's disease were 90.4% (95% CI: 85.4–93.9) and 83.0% (95% CI: 77.0–87.7), respectively (Figure 2).

Discussion

In this study, we performed a comprehensive evaluation of first-time registered Darier's disease in the Danish nationwide hospital patient register, DNPR, covering the period from 1977 to 2018. We found overall PPVs of above 80% for both probable and confirmed Darier's disease, with little variation in subgroups of sex, age at diagnosis, year of diagnosis, and type of hospital contact. These findings emphasize a consistent relatively high level of accuracy in the diagnoses of Darier's disease at Danish dermatological departments.

We found the lowest PPV among the small group of eight patients who had Darier's disease registered as a secondary diagnosis, which may indicate that secondary diagnoses are registered with less caution and fewer details in the medical record enabling a positive validation of the secondary diagnosis. We observed lower PPVs for diagnoses recorded in the calendar period of 2001–2008 than for 1977–2000 and 2009–2018. The reason for this apparent difference is unclear. One possible explanation is chance, another that even at specialized departments, the availability of dermatologist sub-specialized or with special interest in genodermatoses may have varied during the study period. A priori, we had expected that diagnostic advances with time (eg, increased access to genetic

testing) could result in higher PPVs for the most recent period, as well as for the ICD-10 diagnosis code of Darier's disease than the ICD-8 diagnosis code. On the contrary, PPVs for the ICD-8 diagnosis code were numerically slightly higher than for the ICD-10 code. This finding may reflect that a first time diagnosis of Darier's disease is based primarily on the clinical and histological examination with genetic testing serving only as a confirmatory test in most cases. Furthermore, early in the study period, dermatological departments had much higher capacity for inpatients and intensive topical treatment, perhaps increasing time for detailed assessment of patients and their skin leading to higher diagnostic accuracy than what is possible during todays' relatively short outpatient consultations.

Our study has some potential limitations. We restricted the validation sample to patients diagnosed at dermatological departments. However, this choice is in accordance with national clinical guidelines that recommend patients with Darier's disease to be diagnosed and managed at specialized dermatological departments.[15] From that point of view, inclusion of non-dermatological departments seems redundant for the present study and epidemiological investigations using DNPR to study Darier's disease. Indeed, the majority (83%) of first-time diagnoses stemmed from dermatological departments.

For the sake of cost- and time-efficiency of the validation process, which involved multiple departments spread throughout the country, only one investigator conducted the medical record review. Although this approach might have introduced bias of unknown direction, we tried to mitigate such effects using predefined extraction sheets and validation criteria.

Incomplete information from medical records likely led to underestimation of the PPVs, since at least six records contained information suggesting Darier's disease but did not meet the validation criteria. Assuming a best-case scenario where these patients all had Darier's disease, the PPV for probable diagnoses would increase to 92.3% (95% CI: 87.8–95.3).

We were able to evaluate most diagnoses (85.6%), which is an important strength of our study. Furthermore, the similarity of the total population and the validation sample provides some reassurance against selection bias. Although the validation sample included a lower proportion of ICD-8 diagnoses of Darier's disease, this is unlikely to have affected our results since we, as mentioned above, observed higher or similar PPVs than for the ICD-10 diagnosis codes. Another important aspect of data quality is completeness, which we were unable to examine in the present study. Thus, incompleteness of mainly milder cases cannot be excluded as some patients may be managed exclusively at office-based dermatologist who do not report to the DNPR.

To our knowledge, our study reports the largest and most extensive validation of routinely registered diagnoses of Darier's disease. When considering diagnoses from specialized departments, the diagnosis of Darier's disease has higher validity than that of two other genodermatoses, congenital epidermolysis bullosa and inherited ichthyosis, previously validated by our research group.[8,9] This difference is particularly pronounced for confirmed diagnoses, suggesting that the clinical diagnosis of Darier's disease is more accurate than that of the more phenotypically diverse group of patients suspected for either epidermolysis bullosa or congenital ichthyosis. Nevertheless, we note that despite a relatively high PPV for the diagnosis of Darier's disease in the DNPR, some misclassification must be expected and the level of clinical and paraclinical detail is sparse. These limitations underscore the need for highly specialized databases for this disease and further inspires our ongoing efforts to develop and maintain the Danish National Database for Genodermatoses.[16]

Conclusion

The PPVs for first-time diagnoses of Darier's disease reported by departments of dermatology to the DNPR were overall at levels above 80%, making their use acceptable for epidemiological studies. However, when stratifying for subpopulations according to, eg, age or certain time intervals for the year of diagnosis, the PPVs were found to be a little lower making DNPR less suitable for more specified analysis of Darier's disease in such subpopulations. As an alternative to the DNPR, specialized clinical databases, such as The Danish National Database for Genodermatoses,[16] provide a basis for validated cohorts with minimal risk of misdiagnoses.

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Disclosure

The authors declare no conflicts of interest in this study.

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