Oral soft tissue manifestations in HIV-positive vs. HIV-negative children from an inner city population: A two-year observational study

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Abstract

Purpose: Data accrued after two years of longitudinal observation of oral soft tissue lesions in a cohort of HIV-infected children and comparisons to a group of uninfected controls is presented.

Subjects and methods: One hundred and four HIV-positive subjects were enrolled from an inner city pediatric HIV clinic and HIV-negative household peers served as control. Oral exams were performed at six-month intervals while laboratory data of interest were obtained from the children's medical records.

Results: HIV-positive children had significantly more oral soft tissue lesions than their HIV-negative peers. In particular, the prevalence of candidiasis, linear gingival erythema and median rhomboid glossitis were high. However, oral lesions were not good predictors of mortality and only candidiasis was associated with a low CD4 count.

Conclusions: Oral soft tissue lesions were common among HIV-positive children. While candidiasis was correlated with advanced disease, oral lesions were not good predictors of mortality. (Pediatr Dent 22:215-220, 2000)

Despite a recent drop in the number of new cases in the U.S., Human Immunodeficiency Virus (HIV) infection in pediatric populations remains a growing public health concern of the 1990s, particularly among inner city populations and ethnic minorities. While recent advances in therapy and prevention are beginning to show promising results in economically developed countries, the number of pediatric infections worldwide has been growing at an alarming rate: an estimated 10 million people younger than age 18 will be HIV-infected by the year 2000. Despite therapeutic advances in the US, the mortality rate in pediatric populations continues to be high. Additionally, as survival increases, attention will be focused on improving quality of life through reduction of morbidity. Thus, understanding of manifestations of oral disease will become increasingly important.

The spectrum of clinical manifestations in HIV-infected children differs in important ways compared to their adult counterparts, mostly due to differences in the viral-induced immunopathologic changes in these two different age groups. To date, considerably more study has been dedicated to the latter population, mostly due to the greater number of infected adults. As a result, knowledge of HIV infection manifestations in children is still evolving and few data from longitudinal studies have been published.

In a recent article, Kline has reviewed these data and noted a high frequency of oral lesions in HIV-infected children, with candidiasis being by far the most common oral ailment. He also reported a high prevalence of parotid enlargement and herpetic stomatitis. However, the author acknowledged the lack of information on pathogenesis of HIV-associated oral manifestations in children. The current article presents results from a longitudinal assessment of prevalence of oral soft tissue lesions and their correlations with relevant blood laboratory values, and mortality in a group of mostly ethnic minority pediatric HIV-positive subjects recruited from a specialized care center, compared to a control group of household peers.

In this study, the well-known, more colloquial term “pediatric AIDS” was replaced by “HIV-infected.” Primarily, this latter term is broader and better defines our patient population that included children with little or no effects of the disease, in addition to late stage, immunocompromised subjects. Additionally, we did not want to create the false impression that all enrolled subjects were imminently close to death and physically debilitated. While the CDC classification for pediatric HIV infection was not used as a defining variable, patients were classified by CD4 counts, which, at the time, the study was performed were the best-known surrogate markers for disease progression and mortality.

Methods

This report presents data accumulated on all patients (HIV-infected and controls) enrolled who participated in one or more of the five visits performed over a two-year period. Consecutive examinations for each subject were completed within five to seven months from the previous examination. While not all subjects were present at all five visits (see Results section), analyses of interest included data obtained from all enrolled children. For oral lesion-specific analyses, each lesion on a given subject was counted only once, regardless of the number of visits at
which that lesion was present in the same child or the number of examinations the child had undergone. Baseline assessment of the patients included a complete blood count with differential values (CBCD), CD4 (T4) lymphocyte count, plasma immunoglobulin levels, and a thorough oral soft tissue examination. A trained research assistant extracted all laboratory and medical data from the child’s medical records. Analyses of association of oral lesions with patients’ immune status were based on these baseline values. Demographic data obtained included age, gender, and race. Based upon age at baseline, subjects were divided into three groups corresponding to their stage of dental development: 2-5 years old (primary dentition), 6-11 years old (mixed dentition) and 12-15 years old (permanent dentition). For demographic analyses, only baseline age data were used.

The oral soft tissue examinations were performed by one of two blinded, experienced oral medicine clinicians. These exams were performed in a dental chair using a tongue blade, dental mirror and sterile gauze under adequate lighting. While the patient’s HIV status was not revealed at the visit, the physical condition of some infected patients strongly suggested their seropositivity. Lesions were documented based on their clinical appearance and results were recorded on standardized forms. All soft tissues of the oral cavity, including the lips, buccal mucosa, tongue, soft and hard palate, floor of the mouth, attached and non-attached gingivae, salivary gland, and the oropharynx were thoroughly examined. Fungal and microbial oral cultures were obtained at all examinations from both HIV-infected and control children. Microbiological results are presented and analyzed elsewhere. Following each semiannual examination, all children were referred to dental services and presented and analyzed elsewhere. Following each semiannual examination, all children were referred to dental services and presented and analyzed elsewhere.

Overall, over the two-year period, 76% of the HIV-positive children were treated with one or more reverse transcriptase inhibitors but none received protease inhibitor medication during the study period. Baseline CD4 lymphocyte counts for the HIV-infected group ranged from 0 to 2,147 cells/ml (mean 539 ± 518). The mean percentage of CD4 cells from the total number of lymphocytes was 19% ± 14%, with CD4/CD8 ratios ranging from 0.00-6.77 (mean 0.52 ± 0.80). The mean neutrophil count was 2,120 ± 1,405 cells/ml. Viral loads were not routinely measured for these subjects during the study period. Ninety-four percent of the HIV-infected children were treated with one or more reverse transcriptase inhibitors but none received protease inhibitor medication during the study period.

The frequencies of oral lesions are presented in Table 2. Overall, the two-year period, 76% of the HIV-positive children (n=78) had a lesion at least one examination, as compared to only 36% of the control group. HIV-positive children were approximately twice more likely (odds ratio [OR]=1.98, 95% confidence interval [CI] 1.43-2.75) to have a clinical oral lesion than the control subjects. Virus transmission in the HIV-positive group occurred vertically at birth in 100 cases; the remaining children were infected through blood transfusion (n=1) or factor VIII cryoprecipitate treatment (n=3). For the 171 subjects, age at baseline ranged from 2 to 15 years with a mean of 7.1 ± 3.8 years (6.7 ± 3.8 and 7.8 ± 3.7 for infected and control subjects, respectively); 47% of the subjects were female and 95% were minorities (136 African-American and 26 Hispanic) (Table 1).

Among the minority subjects, 60% (n=82) of the African-American and 54% (n=14) of the Hispanic children were HIV-positive.

Seventy-one percent of the original subjects (n=121, 68 HIV-positive and 53 controls) completed visit five examination (e.g., were followed up for two years). Patient attrition was due to death (n=19), hospitalization of HIV-positive subjects (n=15), or withdrawal of the HIV-negative child from the study due to death of the HIV-positive sibling (n=11); in five cases the cause of no participation is unknown. Loss of subjects was relatively equally distributed across gender, age, and ethnic group categories.

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The number of lesions in the HIV-positive group was 4.2 times greater than in the control group (101 vs. 24 lesions, respectively, P<0.001). The prevalence of all specific oral soft tissue lesions, except conventional gingivitis, was higher in the HIV-infected children. There were significantly more lesions in 12-15 year old children than in the younger groups (P<0.016). In particular, LGE accounted for most of this prevalence disparity, with other lesions more equally distributed.

**Table 1. Distribution of Ethnic Group and Sex by HIV Status at Baseline**

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Male</th>
<th>Female</th>
<th>Total (%)</th>
<th>Male</th>
<th>Female</th>
<th>Total (%)</th>
<th>Total Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>African-American</td>
<td>39</td>
<td>43</td>
<td>82 (79)</td>
<td>33</td>
<td>21</td>
<td>54 (81)</td>
<td>137 (80)</td>
</tr>
<tr>
<td>Latino</td>
<td>7</td>
<td>7</td>
<td>14 (14)</td>
<td>7</td>
<td>5</td>
<td>12 (17)</td>
<td>26 (15)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>4</td>
<td>4</td>
<td>8 (8)</td>
<td>0</td>
<td>1</td>
<td>1 (2)</td>
<td>9 (5)</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>54</td>
<td>104 (100)</td>
<td>40</td>
<td>27</td>
<td>67 (80)</td>
<td>171 (100)</td>
</tr>
</tbody>
</table>
across age groups. No differences in prevalence of lesions were detected in analyses by sex and race.

The mean numbers per ml of CD 4 lymphocytes associated with specific oral lesions are shown in Table 3. Patients with oral candidiasis had fewer CD 4 cells (mean number = 381 and 618 cells/ml for lesion vs. no lesion groups, respectively, \( P < 0.05 \)) and greater IgA levels (mean 435 mg/dl and 229 mg/dl for lesion-no lesion groups, respectively); there were no statistically significant differences between lesion and no lesion groups for all other diagnoses. Similar analyses of neutrophil counts between lesion and no lesion groups also revealed no significant differences.

Of 19 deceased subjects, 17 (89.5%) had baseline CD 4 counts below 200 cells/ml; average CD4 counts were significantly lower in the deceased vs. the surviving group of HIV-positive children (\( P < 0.001 \)). Thirty-two percent of the deceased children (\( N = 6 \)) were diagnosed with a total of 17 oral soft tissue lesions, while the surviving HIV-positive children (\( N = 85 \)) had a total of 84 lesions (Table 4). Surviving HIV-positive subjects were 2.2 times more likely than the deceased group to have had at least one oral soft tissue lesion (68.3% vs. 31.6%). There were no differences in either the neutrophil counts or specific oral lesions prevalence between the surviving vs. deceased HIV-positive groups.

### Discussion

As of June 1998, there were 8,280 reported pediatric AIDS cases and 1,791 reported pediatric HIV cases in the USA (CDC data, www.cdc.gov/nchstp/hiv_aids). Despite effective prophylactic pre-partum therapies, the prevalence of HIV-infections in newborn children may increase due to the increased number of childbearing age female virus carriers. At the same time, with the advent of new, more effective antiretroviral therapies, HIV-infected pediatric populations may have a longer life expectancy and/or a different pattern of disease progression. In this context, it becomes imperative to follow the clinical course of this disease and establish prevalence, morbidity, and prognostic significance of readily accessible signs and symptoms of the oral cavity.

Oral lesions are common among HIV-infected patients, often being the first manifestations of disease progression in these individuals.\(^7\)\(^-\)\(^11\) Recent articles have reported prevalence and morbidity of oral manifestations of pediatric HIV infection.\(^2\)\(^,\)\(^8\)\(^,\)\(^12\)\(^,\)\(^13\) Current literature also suggests that oral manifestations may constitute early clinical signs of this viral disease and could provide independent markers of its progression. Oral clinical manifestations may also have prognostic significance for AIDS-related morbidity and mortality.\(^10\)\(^-\)\(^16\) However, few reports present a clear picture of pediatric oral pathological findings in relation to patients’ immune profile and demographic data, as well as the prognostic value of such findings for development of further complications.

Oral candidiasis

Oral candidiasis, or thrush, was the most common clinical finding in our patient population, which is consistent with other reports.\(^7\)\(^,\)\(^12\)\(^,\)\(^14\) The total number of patients with oral candidiasis included both the pseudomembranous and atrophic clinical presentations. All these diagnoses were confirmed by culture and number of colony forming units. These data are presented elsewhere. Other lesions associated with fungal organisms such as median rhomboid glossitis and angular cheilitis were considered separately due to the incomplete understanding of their etiology.

Patients exhibiting candidiasis had a lower baseline CD 4 count and higher IgA levels, but similar neutrophil counts with HIV-positive children free of candidiasis. While the significance of the difference in immune globulin was not studied, it may point toward an increased Th2 (T helper 2) lymphocyte effect.

### Table 2. Distribution of Diagnosed Oral Lesions (n=number of subjects with the specific diagnosis; individual patients may have more than one diagnosed oral lesion)

<table>
<thead>
<tr>
<th>Lesion</th>
<th>HIV positive (n=104)</th>
<th>HIV negative (n=67)</th>
<th>( P ) (chi sq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candida</td>
<td>23 (19%)</td>
<td>1 (2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pseudomem.</td>
<td>9 (9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrophic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LGE(^a)</td>
<td>23 (22%)</td>
<td>2 (3%)</td>
<td>0.02</td>
</tr>
<tr>
<td>MRG(^a)</td>
<td>13 (12%)</td>
<td>1 (2%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Conventional</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gingivitis</td>
<td>7 (7%)</td>
<td>9 (13%)</td>
<td>0.15</td>
</tr>
<tr>
<td>Necrotizing</td>
<td>4 (3.8%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Periodontitis</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HSV(^a)</td>
<td>3 (3%)</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>Hairy leukoplakia</td>
<td>2 (2%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Other lesions</td>
<td>17 (16%)</td>
<td>10 (15%)</td>
<td></td>
</tr>
<tr>
<td>Total lesions</td>
<td>101</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Patients with lesions</td>
<td>78 (75%)</td>
<td>24 (35%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

\(^a\) LGE=Linear gingival erythema; MRG=Median rhomboid glossitis; HSV=Herpes simplex virus.

### Table 3. Mean CD4 lymphocyte counts at baseline for specific oral lesions at any one of the examinations over the two year period for HIV-positive subjects only (n=104)

<table>
<thead>
<tr>
<th>Lesion</th>
<th>CD4 Count (SD)</th>
<th>( P ) value (( *=)sig)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Present (at least one visit)</td>
<td>Absent (never)</td>
</tr>
<tr>
<td>Candidiasis (n=32)</td>
<td>381 (419)</td>
<td>618 (545)</td>
</tr>
<tr>
<td>LGE (n=23)</td>
<td>417 (495)</td>
<td>583 (523)</td>
</tr>
<tr>
<td>Conv. gingivitis (n=7)</td>
<td>326 (307)</td>
<td>727 (561)</td>
</tr>
<tr>
<td>M RG (n=13)</td>
<td>846 (546)</td>
<td>672 (559)</td>
</tr>
<tr>
<td>Any lesion</td>
<td>483 (480)</td>
<td>783 (748)</td>
</tr>
</tbody>
</table>
in patients with candidiasis. Thus, we agree with other authors\textsuperscript{16} that this lesion may be a good prognostic factor for disease progression; however, in the current study candidiasis was not an independent predictor of survival outcomes, which appears to be in conflict with previous reports.\textsuperscript{15,16} Further studies of these issues are thus warranted.

Linear gingival erythema (LGE)

LGE has been described in HIV-infected adults as a red marginal gingival banding of uniform color and consistency.\textsuperscript{14} This peculiar clinical presentation was considered by some authors to be a precursor of necrotizing periodontitis and has been reported to occur in 11-38\% of HIV-positive populations.\textsuperscript{18-21} Histological and microbiological studies have associated LGE with changes in tissue immune cell composition and a possible fungal (candida) etiology.\textsuperscript{18-21} However, more recent studies reported no differences in gingival banding prevalence in HIV-infected versus non-infected groups.\textsuperscript{22} In the current study, LGE was also identified in two non-infected (ELISA negative) patients, which suggests that this clinical entity is not confined to HIV-positive patients. However, prevalence of this lesion was significantly higher for HIV-infected children. LGE has been described previously in HIV-infected pediatric populations, but prevalence has been low.\textsuperscript{11,14} The much higher prevalence of this lesion presented here could be explained by the older average age of our pediatric population. Indeed, the prevalence of LGE was significantly higher in the older age group (12-15 years old), and this prevalence is consistent with that reported in adult populations. Also consistent with previous reports,\textsuperscript{21} the current study data show a trend toward a lower CD4 cell count in LGE patients. However, since LGE has only been defined on clinical grounds alone and criteria for its diagnosis are neither uniform nor rigorous, comparisons with other studies are difficult and conclusions regarding this lesion at the current time would be premature.

Median rhomboid glossitis (MRG)

This relatively common oral lesion has been associated with candida colonization but its complete etiology remains unclear. Curiously enough, the authors found no other studies of oral manifestations of pediatric HIV mentioning MRG. In the present study, this lesion was the third most prevalent (n=13) in HIV-positive children and was not identified in the control group which suggests a possible association of MRG with immune dysfunction in pediatric populations. However, unlike candidiasis, no significant differences were observed in baseline CD4 or neutrophil counts in HIV-positive children with MRG as compared to the others. In fact, the CD4 counts in MRG-diagnosed children were slightly higher. While these findings need confirmation, they also suggest that MRG should not be considered a form of candidiasis and should be analyzed separately.

Conventional gingivitis (CG)

This condition was diagnosed on clinical grounds alone, and consisted of gingival inflammation in the absence of attachment loss, necrosis, or gingival erythematous banding. While CG was the most prevalent oral soft tissue lesion in the control group of children, constituting 38\% of all lesions (n=9), it only accounted for 7\% of the lesions in the HIV-positive group. This

<table>
<thead>
<tr>
<th>Table 4. Immune Cell Counts and Specific Oral Lesions in Deceased vs. Alive HIV+Subjects</th>
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<tbody>
<tr>
<td>Deceased (N=19)</td>
</tr>
<tr>
<td>Mean CD4/ml (SD)</td>
</tr>
<tr>
<td>Mean neutrophil (SD)</td>
</tr>
<tr>
<td>Candidiasis</td>
</tr>
<tr>
<td>LGE</td>
</tr>
<tr>
<td>MRG</td>
</tr>
<tr>
<td>Other lesions</td>
</tr>
<tr>
<td>Total subjects with lesions</td>
</tr>
</tbody>
</table>

Fig 1. Linear Gingival Erythema (LGE) in an 8-year old female. Note the absence of inflammatory swelling.

Fig 2. Conventional (plaque-induced) gingivitis in a 17-year old female. The gingiva is swollen as a result of inflammation.

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Deceased (N=19) Living (N=85) P value
Mean CD4/ml (SD) 122 (364) 656 (496) <0.001
Mean neutrophil (SD) 1980 (1379) 2164 (1421) 0.62
Candidiasis 6 26 0.58
LGE 6 17 0.66
MRG 2 11 0.81
Other lesions 3 30 0.11
Total subjects with lesions 6 72 0.002

Median rhomboid glossitis (MRG)

This relatively common oral lesion has been associated with candida colonization but its complete etiology remains unclear. Curiously enough, the authors found no other studies of oral manifestations of pediatric HIV mentioning MRG. In the present study, this lesion was the third most prevalent (n=13) in HIV-positive children and was not identified in the control group which suggests a possible association of MRG with immune dysfunction in pediatric populations. However, unlike candidiasis, no significant differences were observed in baseline CD4 or neutrophil counts in HIV-positive children with MRG as compared to the others. In fact, the CD4 counts in MRG-diagnosed children were slightly higher. While these findings need confirmation, they also suggest that MRG should not be considered a form of candidiasis and should be analyzed separately.

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difference was largely due to the fact that the latter group had so many other lesions. However, there were no differences in prevalence between the control and HIV-positive groups, or in laboratory values between HIV-positive children with and without CG. Thus, this condition appears to be unrelated to the HIV infection.

Other lesions
Prevalence of other oral lesions was low and did not allow for adequate statistical analyses. Necrotizing periodontitis (n=4), recurrent aphthous ulcers (n=4), and hairy leukoplasia (n=2) were found only in seropositive individuals while HSV (n=4) and oral papilloma (n=3) were identified in both groups. In contrast with other reports,7 we identified only one case of paediatric Kaposi sarcoma.13,23 This discrepancy could be due to socio-geographic differences in the respective studied populations.

Demographic differences
Demographic analyses with regard to gender, age and race revealed few differences: the larger proportion of lesions, particularly LGE, in the older children can be attributed to the longer duration and greater severity of their immunosuppressive disease and/or age-related changes in oral flora. There were no differences observed between the HIV-positive various racial groups (P=0.29). Finally, all differences between genders were also insignificant. These findings are not surprising, since most patients had similar socioeconomic backgrounds and biological differences between pediatric males and females are minimal.

Mortality
The proportion of each of the specific oral lesions was not significantly different in the deceased group of patients from the group of surviving HIV-positive patients. Similar to the general prevalence, the most common lesions in the deceased group were candidiasis and LGE, which together accounted for 12 diagnoses. Unlike other studies that reported an association between oral candidiasis and survival, the current data suggest that specific oral lesions are not consistent prognosticators of mortality in this group of patients. The only significant differences between deceased and surviving HIV-positive patients consisted of their total number of oral lesions and their baseline CD4 cell counts, which were both larger in the surviving group. While the latter finding confirms the established predictive value of CD4 counts, the former is surprising and not easily explained. However, since some of the deaths occurred early in the study, a longer time was allowed for diagnoses of lesions in the surviving population. The significance of this fact was not analyzed.

The reported population has the largest number of HIV-infected children to undergo this study. However, since nearly all of the subjects were ethnic minorities who were infected at birth, results presented here should be interpreted with caution and may not apply to other groups of children. Additionally, since the patient population was recruited from a specialized health care center, HIV-positive children typically received excellent medical management of their disease, including treatment for oral signs and symptoms. Thus, specific lesions may have been diagnosed early and treated between the semianual oral examinations, raising the possibility of a type II statistical error. Two additional limitations of this study are the relatively infrequent visits for observation and the fact that, with the exception of candidiasis, lesions were diagnosed solely on clinical criteria. Nevertheless, results presented here may be the best obtainable in a pediatric group of immunocompromised patients.

This study identified prevalence of specific oral lesions, as well as their correlations with CD4 and neutrophil counts and mortality, in the studied population. These findings may help clinicians tailor therapeutic interventions but are mainly intended as the basis of further studies of clinico-pathologic associations and intervention strategies. As high-potency combination antiretroviral therapy becomes increasingly the standard of care for HIV-infected children, clinicians report slowing of disease progression and improved immune function. Ongoing prospective evaluation of this patient cohort will provide further information on the impact of such treatment on oral manifestations of HIV infection.

Conclusions
1. Oral soft tissue lesions were common among HIV-infected children;
2. The prevalence of these lesions was significantly higher in HIV-infected patients than in non-infected controls;
3. Oral lesions were not a good predictor of mortality in the studied population;
4. Candidiasis, LGE, and MRG were the most common lesions in the HIV-infected group;
5. Oral candidiasis was associated with lower CD4 counts but not with higher mortality;
6. LGE was diagnosed predominantly in older children, but no other demographic differences were found.

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References

**ABSTRACT OF THE SCIENTIFIC LITERATURE**

**EFFECT OF DIAGNOSTIC THRESHOLD ON EPIDEMIOLOGICAL CARIES**

Modifying the diagnostic criteria typically used in surveys of caries prevalence, the authors state, does not adversely affect the reliability or benchmark validity of experienced examiners to a significant degree. The purpose of the study was to investigate whether such surveys can be tweaked to take more early manifestations of dental disease into account, but without skewing the results from examiner to examiner.

**Comments:** While the methodology of this study is meticulous and the results sound, the most logical conclusion from a practical standpoint is that it largely highlights the continuing difficulty in attempts to predict caries prevalence and cariogenic criteria. There is simply no material in this study to indicate how this result might make a significant difference in the real world, although this paper may make a contribution in the cumulative effort to arrive at an approach that does.

SJM

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36 references