Psoriasis and Male Infertility: A Complex Relationship

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Introduction

- Psoriasis is a chronic inflammatory skin disease affecting 2% of the global population.
- It presents as red, scaly plaques on the skin due to accelerated turnover of keratinocytes.
- Elevated pro-inflammatory cytokines (e.g., TNF-alpha, IL-17) indicate systemic inflammation.
- Psoriasis is associated with joint and cardiovascular issues, making it a multisystemic disease.

Male Infertility and Psoriasis

- Male infertility affects 15-20% of couples worldwide.
- Causes include pre-testicular (hormonal), testicular (structural), and post-testicular factors.
- Systemic inflammation, like that in psoriasis, can impair spermatogenesis.
- Elevated cytokines (IL-6, IL-17, TNF-alpha) in seminal fluid correlate with reduced fertility.

Study Goals

- Investigate the relationship between psoriasis and male infertility.
- Identify comorbidities associated with both conditions.
- Explore temporal patterns and potential causal pathways.
- Provide insights for personalized treatment strategies.

Data and Methods

- **Data Source:** CLALIT Health Services Israeli database (2002–2022).
- **Cohort:** 280,450 patients equally divided between psoriasis and control groups.
- **Key Features:**
  - Date of birth, sex, psoriasis diagnosis date.
  - 122 comorbidities, including infertility.
- Ensure anonymity and balanced gender distribution (50% male, 50% female).
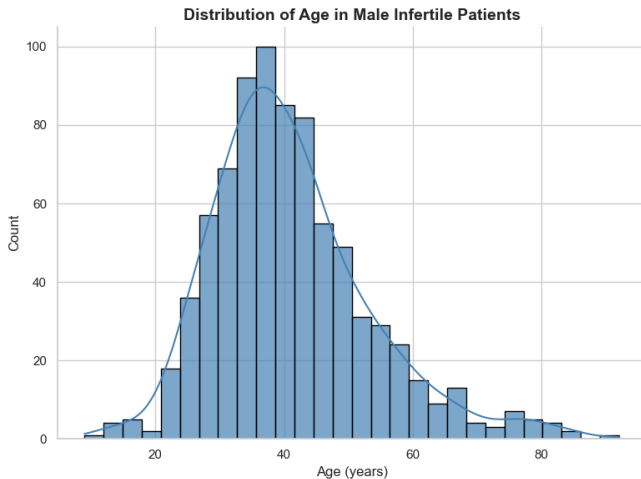
Age Distribution

- **Overall:** Mean age = 43 years (range: 0–103), SD = 21.
- **By Gender:**
    - Males: Mean = 43.5, SD = 20.6
    - Females: Mean = 42.5, SD = 21.3
- **Infertility:** Concentrated in men aged 30–50, mean age = 40.95.

Age Distribution
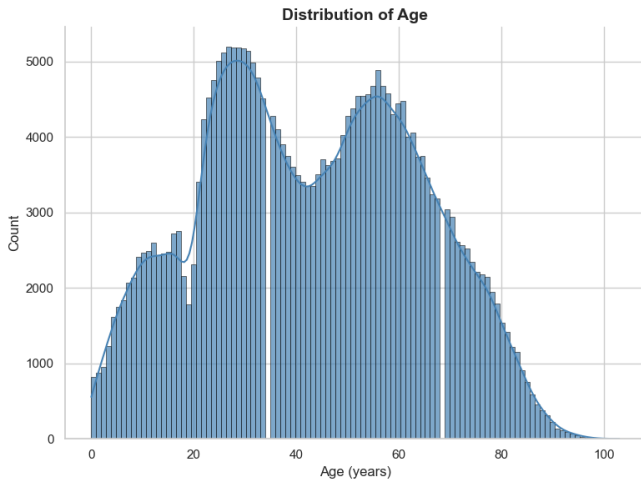
Figure: Age Distribution with, potentially, two modes.

Age Distribution

Figure: Age Distribution in Male Infertile patients.

Comorbidity Analysis: Psoriasis vs. Control

- Prevalence Differences between Psoriasis and Control Groups.
- Statistical tests (Chi-squared, Wilson score) identified significant comorbidities.
- **Key Findings:**
  - Hyperlipidemia (46.1% vs. 42.4%, $p < 10^{-86}$).
  - Obesity (27.5% vs. 22.5%, $p < 10^{-208}$).
  - Diabetes (18.4% vs. 16.3%, $p < 10^{-22}$).
  - Hypertension (29.3% vs. 26.5%, $p < 10^{-61}$).

Comorbidity Analysis: Psoriasis vs. Control

Comorbidity	Psoriasis Prevalence (%)	Psoriasis CI (%)	Control Prevalence (%)	Control CI (%)	Chi2	p-value	dof
Hyperlipidemia	46.085933	[45.83, 46.35]	42.386878	[42.13, 42.65]	388.757687	1.542878e-86	1
Smoking	39.061508	[38.81, 39.32]	35.277590	[35.03, 35.53]	429.692589	1.895815e-95	1
Hypertension	29.318595	[29.08, 29.56]	26.524514	[26.29, 26.76]	271.835825	4.516521e-61	1
Obesity	27.520057	[27.29, 27.75]	22.482439	[22.26, 22.70]	948.652692	2.603845e-208	1
Arthropathy	25.356392	[25.13, 25.58]	21.798538	[21.58, 22.02]	492.355620	4.377826e-109	1
Diabetes	18.441077	[18.24, 18.64]	16.275272	[16.08, 16.47]	229.110050	9.320245e-52	1
IHD	12.237475	[12.07, 12.41]	10.814049	[10.65, 10.98]	139.169437	4.044290e-32	1
Malignancy	11.172045	[11.01, 11.34]	10.151542	[9.99, 10.31]	76.550694	2.146320e-18	1
Reflux Esophagitis / Gastritis / Deudenitis	10.279194	[10.12, 10.44]	8.557675	[8.41, 8.71]	243.355210	7.296938e-55	1
Hypothyroidism	9.409877	[9.26, 9.56]	8.006418	[7.87, 8.15]	173.538354	1.248533e-39	1
Other Neurological Disease	8.691032	[8.54, 8.84]	7.900160	[7.76, 8.04]	57.542175	3.308094e-14	1
Depression	8.509895	[8.36, 8.66]	7.478695	[7.34, 7.62]	101.224427	8.213023e-24	1
other kidney Disease	8.283116	[8.14, 8.43]	7.520057	[7.38, 7.66]	55.992970	7.273061e-14	1
Asthma	8.250312	[8.11, 8.40]	7.129970	[7.00, 7.27]	123.811641	9.263255e-29	1
Arrhythmia	7.950793	[7.81, 8.09]	7.330362	[7.20, 7.47]	38.157218	6.526785e-10	1
Osteoporosis	7.817436	[7.68, 7.96]	7.445177	[7.31, 7.58]	13.730814	2.109647e-04	1
Anxiety	6.211446	[6.09, 6.34]	5.283651	[5.17, 5.40]	111.238713	5.245809e-26	1
Prostatic Hypertrophy	5.928329	[5.81, 6.05]	5.100374	[4.99, 5.22]	92.087399	8.293175e-22	1
Disability	5.855589	[5.73, 5.98]	6.076663	[5.95, 6.20]	6.068548	1.376101e-02	1
Chronic Renal Failure	5.646639	[5.53, 5.77]	5.413443	[5.30, 5.53]	7.253668	7.075633e-03	1
Peptic Ulcer	5.298627	[5.18, 5.42]	4.837226	[4.73, 4.95]	30.929031	2.676382e-08	1
COPD	4.600464	[4.49, 4.71]	3.679087	[3.58, 3.78]	149.755169	1.960985e-34	1
Glaucoma	4.319487	[4.21, 4.43]	4.002853	[3.90, 4.11]	17.546685	2.803390e-05	1
CHF	4.108397	[4.01, 4.21]	3.868069	[3.77, 3.97]	10.512793	1.185509e-03	1
Retinopathy	3.919415	[3.82, 4.02]	3.710465	[3.61, 3.81]	8.285427	3.996451e-03	1
PVD	3.214833	[3.12, 3.31]	2.702799	[2.62, 2.79]	63.842340	1.347854e-15	1
Dementia / Alzheimers / OMS	2.831877	[2.75, 2.92]	3.314673	[3.22, 3.41]	54.700711	1.403555e-13	1
Deafness	2.725620	[2.64, 2.81]	2.442503	[2.36, 2.52]	22.212738	2.440493e-06	1
Neuroses	2.632911	[2.55, 2.72]	2.353361	[2.28, 2.43]	22.424197	2.186025e-06	1
Carotid Artery Disease	2.208593	[2.13, 2.29]	1.822785	[1.75, 1.89]	52.644377	3.997538e-13	1
Other Endocrine and Metabolic Disease	2.194331	[2.12, 2.27]	1.829916	[1.76, 1.90]	47.038986	6.958860e-12	1
OncBreat	2.145124	[2.07, 2.22]	1.991799	[1.92, 2.07]	8.061245	4.522211e-03	1
Joint Replacement	2.142271	[2.07, 2.22]	1.842040	[1.77, 1.91]	32.215069	1.380161e-08	1
Other Hematologic Dis (excl. Iron Def Anemia)	1.975397	[1.90, 2.05]	1.799964	[1.73, 1.87]	11.556456	6.751440e-04	1
Gout	1.513995	[1.45, 1.58]	1.241576	[1.18, 1.30]	38.092378	6.747320e-10	1
Rheumatoid Arthritis	1.399893	[1.34, 1.46]	0.801569	[0.76, 0.85]	230.016148	5.913179e-52	1
Hyperthroidism	1.345694	[1.29, 1.41]	1.256552	[1.20, 1.32]	4.269306	3.880677e-02	1

Figure: Table of differences in Comorbidity Prevalence, Psoriasis versus Control. Statistically significant intervals at 5% alpha error.

Longitudinal Analysis: Psoriasis First

- Evaluated comorbidities developing after psoriasis diagnosis.
- Statistical tests (Chi-squared, Wilson score) identified significant comorbidities.
- **Key Findings:**
  - Hyperlipidemia: 15.7% vs. 0.23%, $p < 0.00001$.
  - Obesity: 11.3% vs. 0.21%, $p < 0.00001$.
  - Hypertension: 6.1% vs. 0.14%, $p < 0.00001$.
  - Depression: 2.1% vs. 0.03%, $p < 0.00001$.

Pre-Existing Comorbidities as Predictors

- Evaluated comorbidities developing before psoriasis diagnosis.
- Certain conditions increase the likelihood of developing psoriasis.
- Presence of Bilateral Effect of certain comorbidities, thus increasing likelihood of Psoriasis development and being aggravated by Psoriasis Onset in feedback Loop.
- **Key Predictors:**
  - Smoking: OR $= 255$x, $p < 0.00001$.
  - Hyperlipidemia: OR $= 247$x, $p < 0.00001$.
  - Obesity: OR $= 310$x, $p < 0.00001$.
  - Hypertension: OR $= 209$x, $p < 0.00001$.

Pre-Existing Comorbidities as Predictors

Comorbidity	Psoriasis Prevalence (%)	Psoriasis CI (%)	Control Prevalence (%)	Control CI (%)	Chi2	p-value	dof
Smoking	30.832357	[30.29, 30.98]	0.176603	[0.06, 0.18]	11583.956982	0.000000e+00	1
Hyperlipidemia	24.703560	[24.38, 29.03]	0.102391	[0.07, 0.15]	8843.710999	0.000000e+00	1
Obesity	15.459621	[15.23, 15.74]	0.052047	[0.03, 0.09]	5204.731206	0.000000e+00	1
Arthropathy	14.553287	[14.29, 14.82]	0.062756	[0.04, 0.10]	4851.099129	0.000000e+00	1
Hypertension	12.534759	[12.29, 12.74]	0.066658	[0.04, 0.10]	4104.107285	0.000000e+00	1
Asthma	7.068451	[6.88, 7.26]	0.006608	[0.00, 0.02]	2244.239251	0.000000e+00	1
Diabetes	6.823078	[6.64, 7.01]	0.049644	[0.03, 0.08]	2129.169363	0.000000e+00	1
Reflux Esophagitis / Gastritis / Deudenitis	4.888558	[4.73, 5.05]	0.023131	[0.01, 0.05]	1513.262278	0.000000e+00	1
Hypothyroidism	4.699814	[4.54, 4.86]	0.026424	[0.01, 0.05]	1449.648577	0.000000e+00	1
IHD	3.976644	[3.83, 4.12]	0.026424	[0.01, 0.05]	1216.927726	1.277777e-266	1
Malignancy	3.694152	[3.56, 3.84]	0.026424	[0.01, 0.05]	1126.719761	5.147074e-247	1
other Kidney Disease	3.656002	[3.52, 3.80]	0.016515	[0.01, 0.04]	1122.165408	5.025576e-246	1
Depression	3.066030	[3.26, 3.53]	0.019418	[0.01, 0.04]	1035.836984	2.813139e-227	1
Osteoporosis	2.950711	[2.83, 3.08]	0.016515	[0.01, 0.04]	898.310653	2.385941e-197	1
Other Neurological Disease	2.723088	[2.60, 2.85]	0.070212	[0.01, 0.03]	829.057954	2.697037e-182	1
Anxiety	2.715864	[2.60, 2.84]	0.019212	[0.01, 0.03]	826.792525	8.072306e-182	1
Peptic Ulcer	2.257697	[2.15, 2.37]	0.009908	[0.00, 0.03]	695.631148	3.064296e-151	1
Prostatic Hypertrophy	2.164928	[2.06, 2.26]	0.009908	[0.00, 0.03]	667.289700	5.804374e-145	1
Arrhythmia	2.030055	[1.93, 2.14]	0.016515	[0.01, 0.04]	609.752556	1.206394e-134	1
Glaucoma	1.482559	[1.40, 1.58]	0.070212	[0.01, 0.03]	442.355394	3.325293e-98	1
COPD	1.331192	[1.24, 1.41]	0.070212	[0.01, 0.02]	399.825409	6.010604e-89	1
s/p CVA	1.260680	[1.18, 1.33]	0.009908	[0.00, 0.03]	376.319130	7.876888e-84	1
Retinopathy	1.257758	[1.18, 1.34]	0.000906	[0.00, 0.03]	375.437611	1.228161e-83	1
Neuroses	1.234746	[1.16, 1.32]	0.070212	[0.00, 0.03]	366.822409	1.685244e-81	1
Chronic Renal Failure	1.162707	[1.09, 1.23]	0.006606	[0.00, 0.02]	348.576018	8.645601e-78	1
DiscBleed	0.847177	[0.78, 0.92]	0.006606	[0.00, 0.02]	251.722587	1.089712e-56	1
Psychoses	0.717507	[0.66, 0.78]	0.006606	[0.00, 0.02]	212.946467	6.915549e-48	1
Congenital Anomalies	0.668691	[0.63, 0.75]	0.003303	[0.00, 0.02]	205.646181	1.224043e-46	1
CHF	0.668520	[0.61, 0.73]	0.003303	[0.00, 0.02]	199.482260	2.709036e-45	1
Hyperthyroidism	0.654113	[0.60, 0.72]	0.003303	[0.00, 0.02]	195.080564	2.474164e-44	1
Joint Replacement	0.554699	[0.50, 0.61]	0.003303	[0.00, 0.02]	164.733736	1.045883e-37	1
Gout	0.492660	[0.53, 0.54]	0.003303	[0.00, 0.02]	142.770699	6.987309e-33	1
Rheumatoid Arthritis	0.476997	[0.43, 0.53]	0.003303	[0.00, 0.02]	141.016064	1.397159e-32	1
Hepatitis B Carrier	0.446541	[0.40, 0.50]	0.003303	[0.00, 0.02]	131.797964	1.656482e-30	1
OncColon	0.344348	[0.30, 0.39]	0.003303	[0.00, 0.02]	100.668380	1.087479e-23	1
OncProstate	0.336506	[0.25, 0.33]	0.003303	[0.00, 0.02]	84.038860	4.876539e-20	1
Familial Mediterranean Fever	0.286778	[0.25, 0.33]	0.003303	[0.00, 0.02]	83.153325	7.592953e-20	1
Chronic Act/Per Hepatitis	0.352158	[0.22, 0.28]	0.003303	[0.00, 0.02]	73.662989	1.045736e-17	1
Cardiomyopathy	0.230524	[0.20, 0.27]	0.003303	[0.00, 0.02]	59.093951	4.299332e-16	1
OncUrineBladder	0.211784	[0.18, 0.25]	0.006606	[0.00, 0.02]	56.099577	2.493053e-14	1
Hypo/hyperparathyroidism	0.185660	[0.16, 0.22]	0.003303	[0.00, 0.02]	52.548993	4.196478e-13	1
OncOther	0.159433	[0.11, 0.17]	0.003303	[0.00, 0.02]	37.278906	1.023015e-09	1
OncLung	0.060210	[0.07, 0.12]	0.003303	[0.00, 0.02]	26.226477	8.673573e-07	1
OncOral	0.057631	[0.04, 0.08]	0.003303	[0.00, 0.02]	13.841199	1.999305e-04	1
Motor Neuron Disease	0.050427	[0.04, 0.07]	0.003303	[0.00, 0.02]	11.694503	6.267094e-04	1

Figure: Prevalence Differences between Psoriasis versus Control for each Comorbidity. Psoriasis Diagnosis After Comorbidity Diagnosis.

Psoriasis and Infertility: Clustering and Classification

- **Data Import and Preprocessing:**
  - Dataset filtered for male patients.
  - Categorical conditions binarized.
  - Time-based features created (psoriasis vs. infertility diagnosis).
- **Chi-Squared Test for Feature Importance:**
  - Significant comorbidities: Hyperthyroidism ($p = 1.8$e-11), Depression ($p = 1.3$e-5), Diabetes ($p = 4.07$e-2).
  - Multiple Sclerosis ($p = 2.35$e-80), Joint Replacement ($p = 6.42$e-44).
- **Clustering Analysis:**
  - Methods: K-Means, Agglomerative, Gaussian Mixture Model (GMM).
  - Best result: GMM with 2 distinct subgroups, Silhouette score $= 0.8$.

Dimensionality Reduction and Classification Models

- **Multiple Correspondence Analysis (MCA):**
  - Reduced categorical feature complexity.
  - Best results: 10 components, Silhouette score $= 0.85$.
- **Classification Models:**
  - Random Forest Classifier: AUC-ROC $= 0.6088$.
  - StepMix Model: Accuracy $= 48.17\%$, 4 latent classes, Entropy $= 0.51$.
  - Spectral Clustering: Moderate performance.
- **Handling Imbalanced Data:**
  - Used SMOTE to balance classes.
  - Limited improvement in predictive power.

Infertility and Psoriasis: Chronological Inversion

- Analyzed patients developing infertility before psoriasis.
- **Key Findings:**
  - Significant comorbidities ($p < 0.05$):
  - Chronic Renal Failure (p = 0.0193).
  - Arthropathy (p = 0.0072).
  - Hyperthyroidism (p = 0.0058).
  - Diabetes (p = 0.0246).

Comorbidome Analysis: Psoriasis and Male Infertility

- **Logistic Regression:**
  - Compared fertile vs. infertile males with psoriasis.
  - Key findings:
    - Hyperlipidemia: $OR < 1$, $p < 0.001$.
    - Hypertension: $OR < 1$, $p < 0.001$.
- **Psoriasis vs. Control:**
  - No significant comorbidities found.
- **Challenges and Limitations:**
  - Dataset imbalance (3% infertility prevalence).
  - Potential overfitting and limited statistical power.

Refined Comorbidome Analysis: Excluding Missing Diagnosis Dates

- **Revised Logistic Regression:**
  - Excluded patients without psoriasis diagnosis dates.
  - Sample size reduced to 14,528 male psoriatic patients.
- **Key Findings:**
  - Hyperprolactinemia: OR = 33.59 (CI: 4.23–267.19).
  - Peripheral Vascular Disease (PVD): OR = 410.19 (CI: 281–597).
- **Limitations:**
  - Wide confidence intervals due to rare conditions.
  - Control group definition remains challenging.

Matched Cohort Analysis: Age-Based Comorbidity Matching

- **Matching Criteria:**
  - Age-based matching for psoriatic infertile vs. control patients.
  - Only comorbidities developed before infertility considered.
- **Key Findings:**
  - Sample size: 118 matched patients (59 infertility before psoriasis, 59 controls).
  - No statistically significant associations ($p < 0.05$).
- **Limitations:**
  - Small sample size and restricted inclusion criteria.

Conclusions: Key Findings

- No direct causal link between psoriasis and infertility was identified.
- Significant overlap in comorbidities suggests shared risk factors.
- **Key Comorbidities:**
  - Hyperlipidemia, hyperprolactinemia, and peripheral vascular disease (PVD).
  - Renal failure, arthropathy, and hyperthyroidism were also prominent.
- Infertility can precede psoriasis, highlighting complex chronological patterns.

Conclusions: Psoriasis and Infertility Relationship

- While a causal link is unproven, infertility often precedes psoriasis in some patients.
- Comorbidities like renal failure, arthropathy, and hyperthyroidism may mediate this relationship.
- Shared inflammatory pathways suggest common biological mechanisms.

Conclusions: Clinical Implications

- Early screening for metabolic and vascular issues in psoriatic patients can improve outcomes.
- Infertile males with psoriasis should be evaluated for cardiovascular and endocrine disorders.
- Personalized treatment strategies should address both dermatological and reproductive health.
- Consider anti-inflammatory therapies to mitigate infertility risk in psoriatic patients.

Conclusions: Limitations and Future Directions

- **Limitations:**
  - Dataset imbalance (3% infertility prevalence).
  - Limited generalizability due to cohort-specific data.
  - Lack of genetic and environmental factor analysis.
- **Future Directions:**
  - Larger, longitudinal studies are needed for causal inference.
  - Investigate genetic predispositions and environmental triggers.
  - Explore potential therapeutic interventions.
  - Conduct multi-center studies for broader applicability.